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THE INTERRELATIONSHIPS OF THE GLANDS OF INTERNAL SECRETION CONCERNED WITH METABOLISM.*

By C. N. H. Long, M.D., D.Sc.,
PHILADELPHIA.

(From the George S. Cox Medical Research Institute, University of Pennsylvania.)

The title of this lecture embodies three questions. One is, what do we mean by metabolism; secondly, what is the manner in which the hormones influence metabolism; and lastly, do the endocrine glands, by their various secretions, alter the activity of other glands which in turn must lead to deviations in the metabolic processes?

It is obvious at the present time that any attempt to understand these questions fully is impossible. We are not only ignorant of the majority of the finer metabolic changes, but our knowledge of the essential activity of any hormone is very incomplete. Finally, when we attempt to explain the manner in which the activity of one endocrine gland influences that of another, we only too often find ourselves indulging our imagination under the guise of scientific truth.

Nevertheless, I shall attempt to lay before you certain phases of metabolism with which we know the glands of internal secretion to be particularly concerned, and to show how more recent work is beginning to give us some insight into the true nature of glandular interrelationships.

Before proceeding to any discussion of these interrelationships

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it would be as well to refresh our memory on what we mean by metabolism. By this word we signify the sum total of chemical changes which occur in the organism. These changes involve not only oxidation and reduction, but also the synthesis and degradation of a large number of chemical compounds.

The Metabolic Process Considered. It will be impossible to discuss more than a few of these transformations and, furthermore, I intend to limit my remarks to certain changes involving proteins, fats and carbohydrates. The equally important mineral metabolism of the body will have to be largely neglected, partly owing to lack of time, but chiefly owing to the fact that our knowledge of these phases of metabolism is even more incomplete than it is in the case of the above substances.

The most important metabolic changes involving the proteins, fats and carbohydrates are as follows:

A. Carbohydrates of the food or derived from body stores are delivered to the tissues in the form of glucose.

B. Proteins, whether derived from food or mobilized from tissue reserves are converted into amino acids. About one-half of these amino acids are deaminated and converted into glucose in the liver. The remainder are also deaminated, but then probably follow the same metabolic pathway as the fatty acids. Finally, a certain amount of resynthesis of body protein is also carried out from amino acids.

C. The fats are split into fatty acids and glycerol. The latter substance is, we believe, converted into glucose, while the fatty acids are oxidized to CO_2 and H_2O.

While it is not impossible that protein may be metabolized without following the path of glucose or fatty acids, for the purpose of our argument we will assume that this is unusual.

This interconversion of foodstuffs is further completed by the fact that glucose may, under certain circumstances, be converted into fatty acids. The reverse change, the conversion of fat to carbohydrate, although postulated by some authorities, is at present not accepted by the majority of workers in this field.

We have in this manner reduced our study of the metabolism of protein, fat and carbohydrate largely to a consideration of the production of glucose and its utilization, and to the metabolism of fatty acids.

When a certain quantity of glucose, whatever its source, is presented to the tissues, we know that two main transformations result: *a*, a certain portion is oxidized to CO_2 and H_2O; *b*, another portion is converted into glycogen. Part of this glycogen is stored in the liver while a somewhat larger portion appears in the muscles. The liver glycogen is usually held to be simply storage carbohydrate, but there is no doubt that the muscle glycogen is intimately concerned with contraction and follows a different metabolic pathway.

It should be noted that some workers have held the view that a preliminary transformation of glucose to glycogen is a necessary step in its oxidation.

The manner in which the long carbon chains of the fatty acids are reduced to CO_2 and H_2O has been the subject of many brilliant researches by Knopp. This worker has evolved the following scheme: *a*, the beta carbon atom (*i. e.*, the second carbon atom from the carboxyl group) is the point at which oxidation occurs. This removes two carbon atoms from the chain. *b*, this successive lopping off of two carbon atoms finally results in a four-carbon ketoxy or hydroxy acid, *i. e.*, acetoacetic acid or betahydroxybutyric acid. Further oxidation of these acids results in the formation of CO_2 and water.

Now it is around this last stage of fat oxidation, that is of the acetone bodies, acetoacetic acid and betahydroxybutyric acid, that some of the most interesting work in metabolism has been done. Shaffer, from *in vitro* experiments, concluded that for the complete oxidation of the acetone bodies a certain proportion of glucose oxidation is necessary. This has apparently been substantiated for the whole organism by many investigators, and in the hands of Woodyatt and others has formed the basis for the explanation of certain phenomena observed in pancreatic diabetes.

The coupling up of the final stages of carbohydrate and fat metabolism is one of the most interesting and difficult problems of metabolism, particularly since more recent work has tended to cast some doubt upon the whole concept.

We have very briefly outlined some of the major phases of the metabolism of protein, fat and carbohydrate and we now have to consider in what manner these changes are influenced or diverted by the various hormones.

Hormones as Catalysts. The many chemical changes that occur during metabolism take place under practically isothermal conditions. This is rendered possible by the presence in the body of substances which may be grouped under the general term of catalysts.

These biologic catalysts can be divided roughly into four groups:

A. The digestive enzymes such as pepsin and trypsin.

B. The intra- and extracellular enzymes and catalysts, such as arginase, phosphatase and glutathione.

C. The vitamins.

D. The hormones.

In the case of the last two groups, the vitamins and hormones, it has not been definitely established that they bring about their effects by catalytic action, but nevertheless, in the case of ascorbic acid and insulin the evidence at present is highly suggestive that this is the manner in which they participate in the body economy. A further difference of these substances from those in the first

two groups is that they require the presence of intact, living cells for the demonstration of the activity.

Without pressing the analogy between hormones and catalysts too far, it is my intention to outline the effects of certain hormones upon metabolic processes as though these chemical reactions were markedly accelerated or retarded by these substances in the manner in which well defined catalysts have been shown to influence other chemical changes.

The Hormones Influencing Glucose and Fatty Acid Metabolism. In investigating the function of any hormone three methods are usually followed:

A. Study of the effects of complete deprivation by excision of the glands secreting the particular hormone.

B. Study of the effects produced by replacement of the excised gland by a purified preparation of the hormone.

C. Study of the effects produced in a normal animal by the injection of such a purified preparation.

By the use of these methods the following hormones have been demonstrated to exert a marked influence on glucose and fatty acid metabolism.

I. **Epinephrin.** *A.* Removal of all adrenal medullary tissue renders the animal sensitive to insulin, and unable to counteract successfully the effects of exposure to cold by an increased heat production. In addition many of the usual phenomena invoked by pain or emotion are absent. From our point of view, the most interesting effect is the failure of the blood sugar to increase under these conditions.

B. An injection of epinephrin produces the following changes in carbohydrate metabolism: 1, The blood sugar rises and glycosuria may appear; 2, the blood lactic acid increases; 3, the liver glycogen at first is decreased and then increased; 4, the muscle glycogen is converted into lactic acid which is carried to the liver and converted into glycogen. As a result the liver glycogen is finally increased above its initial level; 5, glucose utilization in the tissues is decreased.

Thus under the influence of epinephrin a cycle of the formed carbohydrate elements of the body is established. In other words this hormone effects a redistribution of the carbohydrate of the body by increasing the rate of glycogenolysis both in muscle and liver. It is important to recognize that epinephrin does not stimulate the formation of new carbohydrate from protein, nor can it produce a true diabetes mellitus in an intact animal. In this sense, epinephrin is not a contra-insulin or diabetogenic hormone.

II. **Thyroxin.** *A.* It is well known that total thyroidectomy results in a marked fall in oxygen consumption. It is not so well known that completely thyroidectomized animals exhibit but slight blood sugar responses to epinephrin injection.

B. The injection of thyroxin into normal animals produces a marked increase in oxygen consumption and a depletion of the body stores of glycogen.

The effect of epinephrin upon the blood sugar of animals treated with thyroxin is dependent upon the liver glycogen stores. Thus, so long as liver glycogen is present epinephrin hyperglycemia is exaggerated. When, however, the liver glycogen has been depleted epinephrin has but little effect upon the blood sugar. This apparent interrelationship between the thyroid and adrenal medulla is therefore largely determined by the quantity of liver glycogen present. It is probable, however, that one of the effects of thyroxin is to sensitize the sympathetic nerve endings so that minimal amounts of epinephrin produce very large effects.

In a similar manner there is an apparent relationship between insulin and the thyroid hormone which upon examination is also more reasonably interpreted in terms of the liver glycogen content. Thus small doses of thyroid extract diminish the hypoglycemic action of insulin so long as liver glycogen is present. However, when liver glycogen has been depleted by prolonged thyroid influence, the injection of minimal amounts of insulin will precipitate a fatal hypoglycemia.

It is apparent that, depending upon the condition of the liver glycogen stores when the experiments were made, we might in some cases be led to assume that an antagonistic relationship existed between the thyroid or the adrenal and the pancreas, while in others that the hormones were reinforcing each other. As a matter of fact, what is probably happening is that each hormone is exerting its action independently of the other. The response obtained is determined by the existing conditions and not by the presence or absence of another hormone.

I have dealt at some length with these supposed thyroid, adrenal medulla, pancreas relationships since they have played a not inconsiderable part in the history of diabetes mellitus. The concept was first introduced by Falta, Eppinger and Rudinger, and rapidly became associated with the so-called overproduction hypothesis of diabetes mellitus.

III. **Cortin.** *A.* Complete removal of all adrenal cortical tissue is followed by a condition characterized by loss of sodium from the body, hemoconcentration and death. Very frequently such adrenalectomized animals develop marked hypoglycemia, and usually have depleted liver glycogen stores. Until recently it has been assumed that this hypoglycemia and carbohydrate depletion was a result of the disturbance in the water and salt metabolism, although why this should occur as a result of hemoconcentration has always been difficult to answer. In traumatic shock, for instance, where equally great hemoconcentration is present, the blood sugar is usually increased.

A recent publication by Harrop and his co-workers[1] has done much to clarify the occurrence of hypoglycemia following adrenalectomy. They have found that even if dogs were adequately maintained by cortical extracts or salt feeding they still developed hypoglycemia upon fasting. This indicates that under these conditions the adrenalectomized animal is unable to maintain his blood sugar; in other words, although the salt and water metabolism has been restored to normal, there still exists a defect in the carbohydrate metabolism. The importance of this observation will be more apparent when we discuss the effects of adrenalectomy upon pancreatic diabetes. Up to the present the injection into normal animals of large amounts of a cortical extract capable of maintaining adrenalectomized animals has not been followed by any recognizable changes in metabolism.

IV. **Insulin.** When we consider the effects of total insulin deprivation we are of course at once confronted with the problems of clinical and experimental diabetes mellitus. The sequence of events following total deprivation of insulin are as follows: 1, Hyperglycemia and glycosuria that persist during fasting. 2, An increased nitrogen excretion and the development of a constant proportion between the urinary glucose and nitrogen. This proportion, usually spoken of as the G/N or D/N ratio, is one of the most characteristic features of a total diabetes. It has been interpreted, chiefly by the work of Lusk, to indicate that a constant proportion of the amino acids either from the food or body proteins is converted into glucose. Since, 3, it has been held that glucose oxidation virtually ceases in the absence of insulin, all such glucose formed from amino acids is excreted. 4, Finally, large quantities of the acetone bodies betahydroxbutyric acid and acetoacetic acid appear in the urine.

These facts are well established. It is upon the interpretation of the manner in which these various phenomena are brought about that a wide difference of opinion has arisen. Until recently it has been generally accepted that the increased metabolism of protein and fat was a direct consequence of the endeavors of the organism to meet its metabolic demands in the absence of glucose utilization. This point of view looks upon the failure of glucose oxidation in the absence of insulin as the essential defect. The other metabolic changes follow as an attempt at compensation.

Another group of workers has held a different view. The originators of this theory were Falta, Eppinger and Rudinger and their explanation has come to be spoken of as the "overproduction theory." This group has held that there exists an interrelationship between the thyroid, adrenal medulla and the islands of Langerhans. When insulin is removed a glandular imbalance is established. As a result the activity of the adrenal medulla and the thyroid markedly increases the production of glucose from protein and fat. As a

consequence the body is flooded with glucose and the products of fat metabolism—the acetone bodies. This school has also maintained that the normal capacity of the tissues to utilize carbohydrates persists, but the large amounts of glucose presented to them as a result of the overproduction mechanisms overtax their capacity of utilization and hyperglycemia and glycosuria occur.

Without going into details it may be stated that this original theory has been unacceptable to the great majority of physiologists. In the first place, as I have already indicated, it is unlikely that any such glandular interrelationship exists, and secondly, the view that fatty acids may be converted into glucose is without support.

Nevertheless, this "overproduction hypothesis" has introduced the concept of a glandular imbalance as playing a part in the diabetic syndrome as opposed to the view that hypofunction of the pancreas alone invokes these marked metabolic disturbances, without altering the activity of the other endocrine glands concerned with metabolism.

With these ideas concerning diabetes mellitus before us, let us pass to the consideration of another endocrine gland which until recently had been very much neglected from the point of view of its possible metabolic effects. I refer, of course, to the anterior pituitary. As before, let us first consider the effects of removal of the hormones of this endocrine gland upon the organism.

V. **Anterior Pituitary.** Following hypophysectomy in mammals, birds, amphibia, reptiles and fish, there occurs a most striking atrophy of practically all the endocrine organs. Those most markedly involved are the gonads, thyroid, adrenal cortex and, to a lesser extent, the parathyroids and thymus. It is also probable that the islands of Langerhans are involved in this atrophy, but their anatomic situation makes this rather difficult to decide. One fact to be remembered is that the adrenal medulla, so far as one can judge, is not involved.

In view of these findings it is not remarkable that hypophysectomy results in marked metabolic disturbances. Those reported up to the present are:

A. A decreased metabolic rate and cessation of growth.

B. A lowered blood sugar and the development of hypoglycemia symptoms on fasting.

C. A marked sensitivity towards insulin.

D. A decreased response of the blood sugar to epinephrin injections (Cope and Marks),[2] *i. e.*, resistance to this hormone.

E. A decreased fasting nitrogen excretion (Braier).[3]

F. When glucose is fed a large part of it is unaccounted for in terms of glucose oxidation or glycogen storage (Phillips and Robb).[4]

G. In some animals markedly increased fat deposition (Cope and Marks).[2]

H. An atypical response to phloridzin characterized by decreased glucose, nitrogen and acetone body excretion (Houssay).[5]

It is apparent from a study of this table that in addition to the anatomic changes in the endocrines widespread metabolic disturbances involving protein, fat and carbohydrate are produced by removal of the anterior pituitary. This is suggestive of an equally close functional interrelationship between the anterior pituitary and the various endocrines enumerated above.

The dominant influence of the anterior pituitary is further emphasized by the study of the effects of anterior pituitary extracts injected into hypophysectomized and normal animals. Thus the injection of crude alkalin extracts has been shown to cause both anatomic and physiologic restoration of the gonads, adrenal cortex and thyroid as well as a resumption of growth.

When these crude extracts are injected into normal animals the metabolic rate is increased while at the same time the thyroid becomes hyperplastic. Another striking effect is the development of resistance to insulin.

Houssay[6] has reported that the continued injection of such extracts in normal fed dogs leads in a few days to marked hyperglycemia and glycosuria. In this he is supported by Evans, Bauman and Marine and others. For my own part, up to the present, I have not seen either crude or purified anterior pituitary extracts produce these effects in normal animals and other workers have reported similar negative results. The production of diabetes mellitus in normal animals by anterior pituitary injections is only one of the many important problems that awaits future investigation.

Considerable progress has been made in the fractionation of anterior pituitary extracts by Collip and his co-workers.[7] The following fractions have been obtained: *A*, Growth (+ glycosuric in suitable preparations); *B*, thyrotropic (+ ketogenic) − repair of thyroid in hypophysectomized animals; *C*, adrenotropic (practically free from all others); *D*, gonadotropic. Other effects of pituitary extracts are reported, but so far without extensive purification: *A*, Lactation factor; *B*, parathyrotropic; *C*, pancreatotropic—stimulates islands of Langerhans.

It is not my purpose to comment on the apparent paradox of the presence of this large number of apparently specific hormones in an organ that only contains three distinct types of cells. It is probable, however, that further work will reduce rather than increase the number of these hormones as we gain knowledge not only of their chemical nature, but also of their exact physiologic properties.

There is, however, one feature of the majority of anterior pituitary

hormones that is particularly important. This is the trophic nature of their action. By this we mean that in the case of the hormones affecting the gonads, thyroid, adrenal cortex, it has been abundantly demonstrated that they are without physiologic effect if the gonads, thyroid or adrenals are removed. In other words, they produce their effects upon the organism by stimulating the particular endocrine to pour forth larger amounts of its secretion. Thus the thyrotropic hormone not only causes hyperplasia of the thyroid, but also a condition of hyperthyroidism as a result of the increased amount of thyroid secretion that is liberated into the blood stream. Conversely, removal of the anterior pituitary produces a condition largely due to simultaneous hypofunction of nearly all the endocrine organs. The dominant control of the anterior pituitary over the other glands of internal secretion is probably the most important finding in endocrinology in recent years.

The Anterior Pituitary and Pancreatic Diabetes. We have already noted some alterations in the carbohydrate metabolism of hypophysectomized animals. These are: *a*, the occurrence of hypoglycemia on fasting; *b*, an increased sensitivity to insulin; *c*, an abnormal disposal of ingested carbohydrate. In addition I have suggested to you the concept that in another condition characterized by a markedly abnormal carbohydrate metabolism, to wit, diabetes mellitus, glandular interrelationships may play a part.

It has remained for Houssay and his co-workers to discover the beautiful but intricate relationship between the anterior pituitary and the pancreas as is shown by their effects upon carbohydrate metabolism.

About 1927 Houssay and his associates[8] began the publication of a long series of papers concerning the effects of a previous hypophysectomy upon the diabetes following total extirpation of the pancreas. The first experiments were carried out upon toads; they were however rapidly extended to dogs. The findings in both species were as follows: 1, after pancreatectomy in an hypophysectomized animal the degree of hyperglycemia and glycosuria was much diminished compared with that following pancreatectomy in an intact animal; 2, the nitrogen excretion and the dextrose-nitrogen ratio in the urine were also decreased; 3, ketonuria was markedly reduced and diabetic acidosis and coma did not occur; 4, as a consequence of these changes the animals survived for a long period. The diabetes was not entirely obliterated, but was transformed from a rapidly fatal condition into one of mild degree. Thus dogs which ordinarily only live about 2 weeks after pancreatectomy survived for 6 months or more if the hypophysis were also removed; 5, these animals doubly operated upon were extremely liable to hypoglycemic episodes, especially if fasted—glucose injections being often necessary to save their lives; 6, the carbohydrate tolerance, although not normal, was often greatly superior to that of the control depan-

creatized group; 7, marked loss of weight occurred in all those doubly operated upon that survived long periods and, in fact, these animals ultimately succumbed to inanition. This loss of weight is in part to be attributed to the absence of the external pancreatic secretion and partly to the mild diabetic state that persists; 8, removal of the thyroid before pancreatectomy did not alleviate the diabetes.

In the first experiments upon toads, Houssay[9] was able to show that implantation of the anterior lobe of the pituitary brought about a return of the diabetes to its usual severity. Similar experiments in dogs were at first unsuccessful; but in more recent work with alkalin extracts of bovine anterior pituitaries, Houssay was able to exaggerate markedly the diabetic state of his doubly operated dogs, as evidenced by the increased excretion of glucose and acetone bodies.

These remarkable results have been confirmed by several workers upon the dog, while Lukens and I[10] have shown that an equally large amelioration is observed in the severe diabetes that occurs in cats following pancreatectomy.

It will also be realized that these findings point to a participation of the anterior pituitary gland in the metabolic disturbances following pancreatectomy. In other words the "overproduction hypothesis" of diabetes mellitus receives some confirmation. Too much credit should not be given to the original exponents of this view, since: *a*, it is the anterior pituitary and not the adrenal and thyroid that are antagonistic to the pancreas; *b*, as we shall see, carbohydrate utilization is not greatly improved by hypophysectomy and *c*, there is still no decisive evidence that fatty acids can form glucose.

During the last 2 years Dr. Lukens and I have been carrying out experiments upon the mechanisms by which hypophysectomy produces its effects upon an experimental diabetes.

It has been our opinion that the best method to employ would be to study one species of animal and by the use of a sufficient number determine what was the usual response to a total pancreatectomy. We have also made observations upon a number of factors involved in the diabetic syndrome, that is, upon *a*, survival, *b*, degree of hyperglycemia and glycosuria under fasting and fed conditions, *c*, development and degree of ketonuria, *d*, clinical course and mode of death. In this manner we arrive at a standard against which the effects of any procedure upon experimental diabetes can be judged.

We have received ample confirmation that hypophysectomy not only increases the survival of depancreatized cats, but also results in a markedly lower glucose, nitrogen and ketone excretion under fasting conditions. Since acidosis and ketosis do not occur in such animals the increased survival must be largely due to the removal

of factors that normally precipitate them. It should be emphasized that the diabetic state is not completely remedied by hypophysectomy. In the cat particularly it is merely transformed from one of great severity accompanied by intense ketonuria to one of mild degree without ketonuria.

As we have already mentioned, the final stages of fatty acid metabolism are held to be intimately coupled with the oxidation of a certain proportion of glucose. Furthermore, another apparently well grounded hypothesis is that in the absence of insulin glucose oxidation is virtually absent.

In the case of the hypophysectomized and depancreatized animal two questions arise, either of which challenges one or the other of the above concepts. *A*, Is the disappearance of ketonuria due to the resumption of sufficient carbohydrate utilization to complete these final stages of fatty acid metabolism; or *B*, in the absence of the hypophysis is the metabolism of fatty acids completed even though the amount of carbohydrate oxidation is not altered?

If the removal of the hypophysis allows the amount of carbohydrate oxidation to increase, then the view that the sole defect in diabetes mellitus is failure of carbohydrate oxidation is placed in jeopardy. On the other hand, if carbohydrate oxidation is not improved by hypophysectomy then the view of the necessity of the coupling of this process with acetone body utilization is one that applies only under a definite set of conditions.

We have therefore carried out a number of experiments to determine to what extent carbohydrate utilization is improved by hypophysectomy.

In the first group we gave 3 gm. of glucose intraperitoneally to hypophysectomized-depancreatized cats and found that this was followed by a typically diabetic response of the blood sugar.*

In the next experiments we placed the animals on a constant diet and after a suitable fore period added 6 gm. of glucose to the diet. The recovery of the added glucose was quantitative, exactly as it is in the totally depancreatized animal.

Finally we placed the animals on a protein-fat diet and determined the glucose and nitrogen excretion. From the urine nitrogen excretion it is possible to calculate what the glucose excretion should be if 45% of the protein is converted into this carbohydrate. This proportion is taken since the glucose-nitrogen ratio of the totally depancreatized cat is 2.8 to 1. The difference between the calculated amount of glucose and that actually found should represent the glucose derived from protein that is retained in the body. Although we found that this is often a considerable part of the

* It has been observed that when these animals are exhibiting hypoglycemia "normal" glucose tolerance curves may be obtained. More extensive investigations of the respiratory metabolism under these conditions are indicated.

glucose derived from the metabolized protein, yet in reality it only amounts to about 1 to 2 gm. per kilo a day.

The most important test is the change in the respiratory quotient when glucose is given. So far we have not carried this out in our cats, but Houssay[11] has made some determinations upon his dogs. Although he concludes that there is a significant increase in the respiratory quotient, many of us would hesitate to draw conclusions from the small changes he reports in the majority of animals. Furthermore, with one exception, typical diabetic blood sugar curves were found to follow the ingestion of glucose.

I think it is best that for the present we assume that hypophysectomy does not produce any major alteration in the utilization of carbohydrate. In other words, the defect produced in carbohydrate utilization by the deprivation of insulin is not restored by withdrawal of the hypophyseal hormones.

What then is the nature of the alteration produced in the diabetic metabolism? It is at least twofold. *A*, The absence of severe ketonuria, as we have already noted, implies that either acetone bodies are not produced in their usual large quantities or else their complete utilization is restored. Experiments to decide between these alternatives have not yet been done. *B*, the markedly decreased urinary glucose and nitrogen excretion indicates that the usual increased formation of glucose from protein (gluconeogenesis) that occurs when the pancreas is removed is much reduced.

Are the Other Endocrine Glands Involved in the Diabetogenic Action of the Anterior Pituitary Hormones? We have already pointed out that in a large number of instances the anterior pituitary hormones exert their effect by a trophic control of the secretion of another endocrine gland. Is this so in the case of the diabetogenic activity of the anterior pituitary? Before proceeding it would be as well to define what we mean by diabetogenic activity. I have chosen to speak of it here as the capacity of anterior pituitary extracts to increase the glucose, nitrogen and acetone body excretion of a hypophysectomized-depancreatized animal.

If the diabetogenic activity is a trophic one, over what glands of internal secretion is this effect exerted?

There are at least three possibilities. *A*, The thyroid. Houssay[5, 8] has shown that pancreatic or phloridzin diabetes appears to its full extent in thyroidectomized animals. It has, however, been claimed that thyroidectomized rats do not develop ketonuria when injected with anterior pituitary extracts. Further work is indicated upon the possibility that the thyroid may be participating in these phenomena. *B*, The adrenal medulla. The discovery of the glycosuric action of epinephrin by Blum in 1891, followed by the views of Falta, Eppinger and Rudinger that the adrenal medulla participated in the pathogenesis of diabetes mellitus focussed attention upon epinephrin as a diabetogenic hormone. All work to date

refutes this view. It is furthermore unlikely that the anterior pituitary produces its effects by stimulation of this organ since the adrenal medulla is not involved in the general glandular atrophy following hypophysectomy. Other reasons for excluding this organ will be given below.

The only remaining endocrine gland to which some participation in metabolism has been assigned is, *C*, the adrenal cortex. The work of Lukens and myself indicates that if the diabetogenic effect of the anterior pituitary is a trophic one, then this trophic effect is probably mediated by the adrenal cortex.*

The Effects of Adrenalectomy Upon Pancreatic Diabetes. We have successfully prepared a number of totally adrenalectomized-depancreatized cats that have survived for 2 to 4 weeks.[12] These animals exhibit an amelioration of the diabetes comparable to that observed in the hypophysectomized-depancreatized group. We have also prepared a series of animals from which only the adrenal medullæ were removed, and at a later date the pancreas. Such animals do not show any amelioration of the diabetic state, thus conclusively demonstrating that it is the removal of the cortex of the gland that is responsible for the effects of adrenalectomy upon experimental diabetes in the cat.

While it is possible that both hypophysectomy and adrenalectomy ameliorate a diabetes by alterations of the metabolism at different points, this is thought to be unlikely. The fact that adrenalectomy and hypophysectomy are of equal efficiency in this respect together with the marked atrophy of the adrenal cortex following hypophysectomy strongly suggest that excision of either of these endocrines is producing its effect on diabetes by alteration of the same phases of metabolism. As a consequence it may be argued that hypophysectomy produces its effects upon experimental diabetes by reason of the accompanying hypofunction of the adrenal cortex. By analogy with the relationship between the hypophysis and the thyroid extracts of the anterior pituitary capable of increasing the severity of the diabetes in hypophysectomized-depancreatized cats should have but little effect in the adrenalectomized-depancreatized animals.

To test this hypothesis we have taken 9 animals of each type and injected them with a potent anterior pituitary extract. Of the 9 hypophysectomized-depancreatized cats, 4 relapsed into diabetic acidosis and coma and died following the injection. Four others exhibited a markedly increased ketonuria, but recovered.

* In connection with this question Houssay and his co-workers[13] have stated that removal of the adrenals, thyroid, gonads or the gastro-intestinal tract does not prevent the hyperglycemic action of anterior pituitary extracts in the toad. These workers found in this animal that the presence of the liver was necessary. In the dog denervation of the adrenals or thyroidectomy likewise did not prevent the glycosuric action of this extract. No experiments are reported upon completely adrenalectomized animals.

One animal tested a few days before death from inanition did not respond.

By contrast, of the 9 adrenalectomized-depancreatized cats receiving the extract, 8 did not show any alteration in the diabetic condition, the other had an increased ketonuria but was proved to possess an accessory cortical body at autopsy.

The effect of the anterior pituitary extract upon glycosuria was not as striking in our hypophysectomized-depancreatized cats as was its effect upon ketonuria. Nevertheless a definite increase in glucose excretion occurred in about one-half the animals, while no comparable alterations were observed in the adrenalectomized group.

Although this result would appear to establish the trophic nature of at least the ketogenic principle of anterior pituitary extracts, yet there is one factor present in the adrenalectomized-depancreatized cats that calls for further consideration. This is: to what extent is this group of animals suffering from a deficiency of the hormone of the adrenal cortex that we know exercises a marked influence over the sodium and water balance of the body?

We have attempted to control this factor in two ways. *A*, All the animals in which the adrenal and pancreatic tissue was excised at the same time have received daily injections of extracts containing the above cortical hormone. It is true that some of our first preparations received what we now know to be inadequate amounts, but nevertheless they all received some, and we have not observed any striking difference except in period of survival between the diabetes of the inadequately and adequately treated animals. *B*, In another series of 4 animals, the adrenals were first removed and the cats were maintained in good health for periods of from 7 to 28 days before pancreatectomy. The ensuing diabetes of this group in no way differed from that of the former, and neither was the severity of the diabetes increased by doubling the daily injection of cortical extract or by the injection of anterior pituitary extract.

These experiments cast doubt upon the possibility that the amelioration of an experimental diabetes is due to a deficiency of the cortical hormone concerned with water and salt metabolism. Taken in conjunction with the experiments of Harrop *et al.* which demonstrated the development of a severe hypoglycemia during fasting in adrenalectomized dogs maintained with cortical extract, they strongly suggest that the defect in carbohydrate metabolism produced by adrenalectomy is due to the absence of some other substance normally present in the adrenal cortex. As further evidence for this point of view it may be pointed out that injection of the salt and water controlling hormone of the adrenal cortex into hypophysectomized animals does not alleviate their disturbed carbohydrate metabolism. Finally, hypophysectomized animals do not exhibit cortical insufficiency due to sodium loss, yet nevertheless show a striking alteration in their response to pancreatectomy.

If this view is correct, then the adrenal cortex may contain at least two hormones: *a*, one, already described, that appears to control specifically the sodium (and water) metabolism and, *b*, this at present hypothetical entity whose function is particularly concerned with the production of glucose from protein and possibly of certain aspects of the metabolism of fatty acids. It should be clearly understood that the existence of a second principle in the adrenal cortex is so far only a matter of inference, since no one has as yet demonstrated the ability of adrenal cortical extracts to reëstablish the fully diabetic condition in adrenalectomized-depancreatized animals. Until such time as this is accomplished it is important to remember that the possibility still exists that adrenalectomy may produce its effect upon pancreatic diabetes by altering the normal secretory activity of the anterior pituitary.

Other Effects of Adrenalectomy Upon Carbohydrate Metabolism. The evidence for the participation of the adrenal cortex in carbohydrate metabolism is not entirely based upon the effects of the removal of the adrenal glands upon experimental diabetes.

As I have mentioned before, hypophysectomized and adrenalectomized animals develop severe hypoglycemia when fasted. In this condition the blood sugar level has to be maintained by the conversion of protein into glucose. It is also significant that such animals have a decreased nitrogen excretion under these conditions.

Since the work of von Mering, it has been known that the injection of the glucosid phloridzin into animals either fasted or on a protein diet caused marked glycosuria, elevated nitrogen excretion and ketonuria. The urinary glucose-nitrogen ratio becomes constant, which has been interpreted to indicate that all the glucose derived from protein has been excreted. The mechanism by which phloridzin produces this condition is probably by altering the permeability of the renal tubules to glucose so that the organism is unable to retain this substance. As a consequence, both protein and fat metabolism are stimulated.

The difference of opinion as to the manner in which these increases are brought about have been the subject of the same controversy as has existed in the explanation of the effects of total pancreatectomy.

Since phloridzin and pancreatic diabetes present to a large extent the same perversions of metabolism, it is not surprising to find that both hypophysectomy and adrenalectomy markedly alter the response of animals to the injection of this glucosid. Thus Houssay and Rietti[8] have shown this to be so in hypophysectomized dogs and Dr. Gerald Evans,[14] in my department, has shown it for adrenalectomized rats. In both instances it has been observed that the degree of glycosuria, nitrogen excretion and ketonuria is much smaller than is found in normal animals.

There is one other condition in which the formation of carbohy-

drate from non-carbohydrate sources has been demonstrated. This was also discovered by Dr. Evans.[15] If rats are fasted for 48 hours their liver glycogen is reduced to a low level (0.3%). On the other hand, if after a preliminary fast of 24 hours in air, they are then placed for a further 24 hours in an atmosphere of 10.5% oxygen the liver glycogen is greatly increased (up to 1.5 gm. %). This increase in liver glycogen is not derived from the muscle glycogen, since this is also slightly increased, and is accompanied by an increased excretion of nitrogen, indicating that this newly formed carbohydrate had its source from protein. Rats from which all adrenal medullary tissue has been removed show the same changes but not if they have been hypophysectomized or adrenalectomized.

We have seen then that four procedures by which glucose formation from protein is stimulated, to wit, pancreatectomy, fasting, phloridzination and exposure to low oxygen tensions, are relatively ineffective in the absence of either the hypophysis or the adrenal cortex.

Glandular Relationships. Cushing has said, "Endocrinology lends itself to two glaring faults, one the popularization of writing on the subject, and the other a tendency of clinical observers to draw upon their fancy in a symptomatology which does not lend itself to precision."

Knowledge of glandular interrelationships is best gained by first acquiring exact information of the physiologic and biochemical changes produced in the organism by hypofunction or hyperfunction of the individual endocrine organs. Secondly, these effects should be placed on a quantitative basis wherever this is possible. In the case of several of the internal secretions this knowledge is at present not available. Finally, the treatment of glandular disorders only becomes possible when the various hormones have been obtained in a relatively pure form and their dosage accurately determined and standardized.

The multiplicity of hypothetical pluriglandular syndromes that have been described, together with the irrational and unphysiologic methods of treatment by pluriglandular prescriptions, has for many years served to discredit a branch of medicine of which none holds greater promise for future advancement.

The time has now arrived when, chiefly by the efforts of physiologists and biochemists, clinical endocrinologists are beginning to cope with the problems of glandular dysfunction in a rational manner.

The excision of an endocrine gland or the injection of large amounts of its hormone gives us a fairly adequate picture of the condition produced by a hypo- or hyperfunction of this particular organ. The effects of hormonal deficiency or excess are complicated by the possibility that these effects are not confined to one particular

endocrine organ, but induce corresponding and simultaneous alterations in the activity of the other endocrines.

From what I have said this is particularly so in the case of the anterior pituitary. The extirpation of this organ or the continued injection of its extracts is followed not only by marked anatomic changes in the other endocrines, but equally great functional alterations. "All pituitary syndromes are essentially polyglandular" (Cushing).

In the case of the anterior pituitary the concept of functional interglandular relationship is fully exemplified, but it should be reiterated that the control of the anterior pituitary is essentially a trophic one and its hormones (with perhaps one or two exceptions) do not directly bring about any physiologic alteration in the organism.

Conversely, gonadectomy, thyroidectomy or adrenalectomy are followed by structural changes in the anterior pituitary. If these anatomic changes are shown to be accompanied by corresponding deviations in physiologic activity then we are confronted by the possibility that alterations in the degree of activity of any endocrine may, through affecting the anterior pituitary, bring about a generalized polyglandular derangement.

We have now to ask ourselves whether these endocrines whose secretions directly alter the bodily functions ever exhibit interrelationships comparable in any way to those manifested by the pituitary. As you are aware, a large number of such relationships between pairs of endocrine glands have been postulated on clinical grounds and in some cases with good experimental background.

In analyzing these types of relationships two possibilities present themselves. *A*, The hypo- or hyperfunction of a particular hormone may so alter the metabolic background of the organism that the secretions of other endocrines produce an abnormal effect. This is particularly well exemplified by the response of the blood sugar to insulin or epinephrin in hyperthyroid states. This response may not only be greatly magnified, but may even be reversed, depending upon the degree of carbohydrate depletion that has resulted from the hyperthyroidism. Under these conditions we cannot assume that hyperthyroidism has induced alterations in pancreatic or adrenal medullary function, indeed, there is no evidence that this ever occurs. *B*, The dysfunction of one endocrine organ brings about changes in the secretory activity of one or more other endocrines. We have already discussed the anterior pituitary relationships of this type but have still to consider interrelationships of this kind among the other internal secretory glands.

It is probably fairest to state that such relationships do exist, but that the evidence advanced for them is in many instances extremely meager. Consequently, it is not profitable at the present time to attempt to analyze the large number of these supposed

interrelationships. The question of their authenticity will have to await the work of future years.

I have repeatedly emphasized the dominant rôle of the anterior pituitary. So extensive is its influence over the endocrine system that no type of glandular interrelationship of the above type can be established without a most scrupulous examination of the possibility that this supposed interrelationship is not in reality linked through the anterior pituitary.

There is still one aspect of hormonal action that should be touched upon. This is the recent concept of Collip[16] of the existence of "anti-hormones." These substances have up to the present been demonstrated in the case of the growth, gonad, thyroid and ketogenic principles of the anterior pituitary. No anti-hormone has so far been demonstrated for an "effector" hormone such as insulin, estrin or parathyroid, and Collip is of the present opinion that anti-hormones are confined to the trophic hormones.

Collip has also introduced the idea that the effectiveness of a trophic hormone is determined by the ratio between its concentration and that of its corresponding anti-hormone. Thus, if the normal effective stimulus to the thyroid is a 2 to 1 ratio between the thyrotropic and antithyrotropic hormones a hyperactive thyroid might be produced by an increase in the amount of thyrotropic substance or by a decrease in the amount of antithyrotropic hormone. If this principle is a correct one, it greatly adds to the possibility of the occurrrence of smaller changes in endocrine function in contrast to the gross changes that must follow complete removal of an organ of internal secretion.

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STUDIES IN DIABETES MELLITUS.

IV. Etiology. Part 1.*

By Elliott P. Joslin, M.D.,
Clinical Professor of Medicine, Harvard Medical School; Medical Director of the George F. Baker Clinic, New England Deaconess Hospital, Boston, Mass.,

Louis I. Dublin, Ph.D.,
Third Vice President and Statistician, Metropolitan Life Insurance Company,

and

Herbert H. Marks,
New York City.

(From The George F. Baker Clinic, New England Deaconess Hospital, and the Statistical Bureau, Metropolitan Life Insurance Company.)

The first three papers[1] presented the main outlines of the changing picture in diabetes throughout the world. Attention is now directed to the diabetic patient, in particular to the group treated by Joslin and his associates at Boston. This diabetic group is unique and valuable because (1) going back as it does to the year 1897, it covers the several periods in which important advances have been made in the knowledge and treatment of diabetes; (2) it is an experience under the observation of a single individual over a period of 35 years; (3) periodic contact has been maintained with practically all these patients; and (4) the size of the group permits numerical analyses which for many items are statistically significant.

After a general description of the group, the major part of the paper relates to the facts on etiology of the disease in this group of patients with emphasis largely on those elements which lend themselves to statistical representation.

General Features of the Group Studied. We believe that this group is a fairly representative cross-section of the diabetic population. It has been recruited chiefly from the middle classes, with others about equally divided between private-room and free patients, although each individual in it was treated as a private patient.

* Part 2 will appear in the July issue of this journal.

Both sexes and all ages were represented, but the number of children is relatively large, because of the senior author's interest in diabetic children. The proportion of males, too, is relatively high, but not to a degree sufficient to bias the experience or the results based thereon. In this regard, it is, in fact, more representative than most reported clinical experiences.

Intensive study has been made of 6357 patients who were discharged from Dr. Joslin's service during the years 1897 to 1928, and in addition 463 diabetic children treated in the period 1929 to 1934, inclusive. For much of this time Drs. Root, White and Marble have been concerned in their study and care. The records of adult patients seen since 1928 also have been used in some instances. The number quoted includes only those patients who were diagnosed as diabetic according to the best current standards. At the beginning, the diagnosis was based upon a definite glycosuria and the typical symptoms of diabetes, loss of weight and strength, polydipsia, polyuria, polyphagia and pruritus. About 1915, when the series had reached 1000 cases, the level of the blood sugar was added to the diagnostic measures and many earlier cases eliminated. As knowledge of its normal and abnormal variations became known, the blood sugar became of increasing importance in the diagnosis and, in 1927, the entire series was reclassified.

The criteria for the diagnosis of diabetes in recent years have been a venous blood sugar of 0.14 mg.% or more fasting and 0.17 mg.% or more after a meal, with a simultaneous glycosuria definitely related to diet. A large number of referred cases who were not diabetic according to the criteria used are excluded from this study. They will be the subject of a later paper.

The group studied includes all the diabetic patients seen during these years, namely, in the hospital (chiefly the New England Deaconess Hospital and recently at its George F. Baker Clinic), at the office and in consultation. The two latter groups, many of whom were seen only once or twice, are fairly large. Despite this, periodic contact has been kept up with all of them either through their physicians or by direct communication. Thus, of the 6357 patients discharged up to the end of 1928, the condition of 6321 (99.4%) was known as of the anniversary date of discharge in 1929. Again, of the 2397 diabetics treated prior to the beginning of insulin treatment in 1922 and traced as of January 1, 1934, information was obtained on 2373 (99%). Thus, even of this group who were seen originally from 12 to 35 years ago, only 24 (1%) were untraced.

Record Card. The record card used in the analysis of this experience is reproduced on p. 761. On it were abstracted from the senior author's records the data pertinent to this study: (1) Essential items of description; (2) family history of diabetes; (3) facts relating to the onset; (4) significant items in the personal history; (5) clinical

FACE:

CHART I.

E. P. JOSLIN, M.D.,
Boston, Mass.

CASE NO. .....

POST-TREATMENT HISTORY OF DIABETICS

1. AGE AT EXAM.: | 2. DATE OF EXAM.: | 3. DATE OF BIRTH: | 4. RESIDENCE OF PATIENT (CITY AND STATE): | 5. CAUSE OF EXAM. INS. ROUT.

6. SEX: | 7. MAR. COND.: | 8. NATIONALITY OR RACE: | 9. OCCUPATION: | 10. DIAGNOSIS: D.M. R.G. P.D. UNC.

11. FAMILY HISTORY OF DIABETES: F. M. CH. S. B. SP. OTHER (SPECIFY)

12. PAST HISTORY (FOR PATIENTS UNDER 10 AT ONSET): AGE AT ATTACK → S.F. R.F. TONS. DIPH. MSLS. MPS. PERT.

13. ONSET: A. DATE B. AGE C. HEIGHT .....FT. .....IN. C S D. WEIGHT .....LBS. D N E. PREVIOUS MAX. WT. .....LBS. D N DATE..... F. SUGAR DISCOVERED DATE.....

14. ETIOLOGY: A. OB. B. HER. C. GLANDULAR D. BILIARY TRACT E. MISC.

15. EXAMINATION:

GEN. APP.: HT.....FT.....IN. C S WT.....LBS. D N THYR. TEETH

PULSE: ART. 0 1 2 3 4 BL. PR. TONS. EYES

HEART: ABD.

LUNGS: DORS. PED. R. L.

16. BLOOD WASS. .....SUGAR: FASTING: .....P.C. .....HRS. ..... | 17. URINE: ALB. .....DIACETIC.....SUGAR.....

18. DISTINCTIVE FEATURES AND COMPLICATIONS:

19. TREATMENT

HOSP. | IF HOSPITALIZED | OPERATIONS | DISCHARGE DATA | INSULIN.....UNITS P

CONSULT. | DATE ADM..... | DIET: .....C.....P.....F.....CAL. P.P.

OFFICE | DATE DIS. | BL. SUGAR: FASTING: .....P.C. .....HRS. ..... N

REVERSE:

POST TREATMENT RECORD

	DATE	HEIGHT (IF UNDER 20)	WEIGHT (IN LBS.)	OCCUPATION	INSULIN (UNITS)	URINE: SUGAR	CONDITION
1		FT. IN. C S	D N				
2		FT. IN. C S	D N				
3		FT. IN. C S	D N				
4		FT. IN. C S	D N				
5		FT. IN. C S	D N				
6		FT. IN. C S	D N				
7		FT. IN. C S	D N				
8		FT. IN. C S	D N				
9		FT. IN. C S	D N				
10		FT. IN. C S	D N				

MORTALITY DATA: DATE OF DEATH

CAUSE: PRIMARY.....

SECONDARY.....

.....

TERMINAL CONDITIONS .....

IF COMA: INSULIN..... .....UNITS

CAUSE.....

findings on examination; (6) summary of treatment on first admission; (7) follow-up history after discharge.

It will be noted that the name of the patient is not abstracted on the record card. The follow-up section of the card permits entries for periodic observations.

Residence. The very great majority of these patients resided in the northeastern section of this country: 85% lived in New England, 67% in Massachusetts, 41% in the Boston Metropolitan District and 14% in Boston itself. Of the 15% who lived outside New England, nearly half came from the three nearby states, New York, New Jersey and Pennsylvania. A negligible proportion came from other parts of the country, and of the few foreign patients, most of them were from the Canadian provinces bordering on New England. This is particularly true in the case of women. The concentration of so large a number of patients within a relatively small geographic area is, in some measure, an indication that this practice gives a good cross-section of the several social and economic classes, but we shall see this more fully later.

Nationality of Patients. The patients were predominantly of native birth; practically all of the children were American born. Of the adults for whom these facts were recorded, 65.9% of the men and 59.1% of the women were native born. This figure excludes, however, a small percentage of Jewish patients of native birth. Jewish patients who have been classified together regardless of their country of origin, form the second largest group, namely, 14.2% of the men and 18.9% of the women. The proportion of Jewish cases was far in excess of their proportion in the population of this area (about 8%).[2] The only other nationalities represented by considerable numbers were Canadians, Irish and English.

The percentage recorded as native born was lower in the later years of this experience than in the earlier years. The increase in the other nationalities was not concentrated in any single racial or national group. The only one to show an important change was the Italian. The percentage of Jewish cases among male patients increased somewhat, but this did not hold for females. The decline in the percentage of native born and the corresponding increase in other nationalities was due, in large measure, to changes in the population from which our material was drawn, and reflects the great wave of immigration in the three decades prior to 1914. The new immigrants have only recently attained, in large numbers, the ages at which diabetes is prevalent.

Occupation. Another feature which stamps the experience as fairly representative is the occupations of the men. As might be expected, these patients include a rather large proportion of proprietors, officials and managers, and members of the professions, particularly physicians. But there is a goodly representation of the common occupations, as, for example, the building trades and

other skilled workers, viz., tailors and printers, clerks, policemen, factory workers, store clerks and salesmen.

TABLE 1.—NATIONALITY OR RACE OF A GROUP OF ADULT DIABETICS. PER CENT OF EACH NATIONALITY OR RACE TO TOTAL OF KNOWN ORIGIN. BY SEX AND CALENDAR YEAR PERIODS. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Nationality or race	Males.					Females.				
	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.
American (white)	65.9	77.0	70.9	66.5	61.3	59.1	69.8	61.5	60.4	56.7
Canadian	5.7	1.1	6.6	3.3	8.2	5.2	1.5	5.3	4.4	6.3
Jewish	14.2	12.2	11.6	14.7	15.2	18.9	18.8	19.2	20.3	17.7
English	2.6	2.2	2.4	2.7	2.7	2.2	...	1.1	1.3	3.3
Irish	3.0	3.9	1.9	3.3	3.1	5.1	6.0	3.2	5.1	5.4
German and Austrian	0.5	...	0.5	0.5	0.5	1.1	0.8	1.1	0.8	1.3
Scandinavian	1.1	0.5	0.5	1.2	1.3	0.8	...	0.4	0.8	1.0
Scotch	1.0	...	0.8	1.7	0.7	1.1	0.8	0.7	0.9	1.4
Italian	1.7	0.5	1.1	1.3	2.6	2.1	...	1.8	1.8	2.7
Russian, Polish and Lithuanian	0.6	...	...	0.2	1.3	0.6	...	...	0.5	0.9
Colored	0.2	0.5	...	...	0.5	0.4	0.8	...	0.3	0.5
Others	3.5	2.1	3.7	4.6	2.6	3.4	1.5	5.7	3.4	2.8
Number of cases:										
Total	2,779	382	400	906	1,091	2,914	263	304	1,032	1,315
Known nationality	2,411	182	378	837	1,014	2,617	133	281	965	1,238

Of 2304 patients whose occupation was definitely known, 18.6% were foremen, mechanics, operatives or laborers in manufacturing industries. Owners and managers in these industries constituted 6.5% of the total. Retail merchants were numerous, 12% of the total; but this is not surprising in view of the large number of Jewish patients. The other large groups of the proprietor class consisted of those in finance and wholesale trades, 7.2%, and farmers, 4.8%. Other sizeable groups in the working class included chauffeurs and teamsters (1.5%), employees of steam and street railroads (1.7%), store clerks and delivery men (5.6%), clerks (4.3%), government employees (2.8%) and domestic and personal service workers (2.4%). The proportion engaged in professional and semi-professional pursuits was large. On the basis of the total with known occupations, the proportion was 21.8%. Naturally, in an experience of this type the number of physicians and surgeons was large, 6.9%. They constitute an important group, (1) because on the whole they follow treatment more carefully, and (2) because end results of treatment can be obtained very readily. The authors believe that next to children this group is the one most worthy of investigation. Important aspects regarding diabetic physicians in this series will be presented in the course of later papers.

Reason for Initial Examination for Diabetes. Most of these patients were first examined for diabetes because of the development of symptoms of the disease. A large number, however, were diagnosed while still symptomless, as a result of examination for life insurance. Of the adult patients first seen between 1897 and

1928, 426 were discovered in this manner. Among men, these insurance cases account for 12.6% of the total and among women, 1%. If we consider only what may be termed the insurable ages, 20 to 64 years, the percentages are 15.9 and 1.3, respectively. Among men, at ages 35 to 44, no less than 21.3% were so discovered. The actual number of patients discovered as a result of an insurance examination has steadily increased, although the proportion of such cases to the total was highest between 1920 and 1924. Of those cases referred for diagnosis, but found to be not diabetic, insurance cases form an even larger proportion, namely, 25.3% of the men and 3.1% of the women. Approximately two-thirds of those referred for diagnosis because of glycosuria on insurance examination were found to be diabetic.

TABLE 2.—DISCOVERY OF DIABETES BY INSURANCE EXAMINATION. PER CENT OF CASES. BY AGE, SEX AND CALENDAR YEAR PERIODS. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Age at examination.	Males.					Females.
	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.	1897–1928.
All ages	12.6	7.0	12.0	14.7	13.0	1.0
20–64	15.9	8.3	14.8	18.7	16.8	1.3
Under 20	0.6	. .	. .	0.8	0.8	. . .
20–34	12.7	12.5	9.7	13.8	13.1	2.8
35–44	21.3	6.3	20.0	28.9	21.4	2.4
45–54	19.1	9.1	17.7	22.6	20.8	0.8
55–64	11.9	6.5	10.5	12.9	13.3	0.8
65 and over	4.3	4.4	5.5	4.0	4.2	0.4
Number of cases	3,124	428	449	1,034	1,213	3,233

These insurance cases are important for two reasons: (1) they tend to be recently developed cases and, consequently, relatively free from complications; (2) the percentage of these cases is highest in adult and middle life, where the disease, if untreated, tends to be somewhat severer than cases in later life. Early diagnosis is, consequently, of vital importance in these cases. Thus, of the adult male insurance cases, 70.6% were between ages 20 and 54 when diagnosed, but only 49.4% of all cases were in this age group. We shall show later the value of early diagnosis of these cases when we compare the mortality among them with that in other cases. The large proportion of these cases discovered early by insurance undoubtedly influenced the results of treatment in this practice.

The Etiology of Diabetes. *Viewpoint and Method of Analysis.* The factors which have been suggested as entering into the etiology of diabetes are many: heredity, obesity, arteriosclerosis, gall-bladder disease, nervous strain, pituitary disease, thyroid disease and other

conditions. It has been suggested even that there are several types of diabetes; that the diabetes of childhood, of middle life and old age are distinct entities. It is the belief of the authors, however, that there is an essential unity in diabetes and that this unifying factor is heredity. The other factors are essentially of the nature of excitants of the disease. Heredity determines the susceptible individuals, but since the disease is rarely, if ever, present at birth, it is reasonable to postulate at least one or more other factors which act to bring out the inherited predisposition. On this basis, the essential difference between the diabetes of the several ages of life may reflect only the typical age incidence of the various excitants.

Some of the factors, moreover, seem more and more to be linked. The nature of this relationship reflects the newer concept of diabetes as involving not only the islands of Langerhans, but other organs, if not the whole endocrine system of the body. Without destroying the validity of this view of heredity as the unifying factor, however, it is possible that isolated cases may have no hereditary background, such, for example, as might be the diabetes resulting from hemochromatosis, although the heredity is unusually strong in this group. Perhaps it is only the hereditarily predisposed hemochromatosis patient who develops diabetes.

This theory of the unity of diabetes is in our opinion correct, but in the present state of our knowledge, not fully demonstrable. Certainly all of the elements which contribute to the proof cannot come out of a purely clinical experience. Much of it depends upon work in several scientific fields, especially in experimental biology, pathology and biochemistry. While much has been or is being done, the fundamental researches are far from complete. Within the limitations described, the present paper seeks to show what light can be thrown on the problem by this clinical experience, supplemented by the results of investigations in the other related fields. Our approach to the problem is through an analysis of the constitutional factors and medical history of the diabetic patient at the onset of the disease. The discussion of heredity is deferred to the next paper because it cannot be treated adequately as part of the present one.

Physical Characteristics at Onset. *Sex.* The first important and striking feature in the makeup of diabetic patients is the peculiar sex incidence of the disease. Of the 9853 patients seen between 1897 and 1933, 4639 were males and 5214 females. The females thus outnumbered the males by 12.4%. There has been a considerable change in this respect as time has progressed. In the early years of this experience there was a marked excess of males, and even up to 1922 the number of male patients was somewhat greater than that of females. Since that date the number of female patients has been larger and the disparity is definitely increasing. Thus, for the years 1925 to 1928 there were 20% more females than

males, but in 1929 to 1933, 30.8%. As compared with the sex incidence in diabetes mortality, the proportion of females in this experience, even in recent years, is low. For, the death rate from diabetes, as we have seen, is 50% or more higher for females than for males, both in the country as a whole, and in Massachusetts. Such differences in the proportions of males and females, however, are common in clinical experiences (Table 3). The preponderance of male diabetics in older and even in some recent clinical experiences is probably due to the greater frequency with which men seek expert medical care. In this particular series it is to some extent due also to the interest of the senior author in younger patients where there is little difference between the sexes in the incidence of diabetes.

TABLE 3.—SEX INCIDENCE OF DIABETES IN RECENT CLINICAL EXPERIENCES.

	Number of patients.		Females per 100 males.
	Males.	Females.	
Joslin (Boston)—1897–1933	4,639	5,214	112.4
1929–1933	1,515	1,981	130.8
1925–1928	1,213	1,456	120.0
1920–1924	1,034	1,128	109.1
1915–1919	449	350	78.0
1897–1914	428	299	69.9
Barach[4] (Pittsburgh)—1925–1935	264	321	121.6
Cammidge[5] (London)—1934*	598	402	67.2
Gotten[6] (Memphis)—1920–1930	88	61	69.3
John[7] (Cleveland)—1921–1927	928	1,058	114.0
1925–1927	469	531	113.2
1921–1925	459	527	114.8
Mayo Clinic:			
Wilder[8]—1931–1934	1,248	958	76.8
Allan[9]—1930	478	362	75.7
Adams[10]—1926*	571	429	75.1
Palmer[11] (Seattle)—1919–1934	333	380	114.1
Sevringhaus[12] (Milwaukee)—1922–1930	252	248	98.4
Wendt and Peck[13] (Detroit)—1919–1929	379	694	183.1
Wright[14] (Clifton Springs, N. Y.)—1926	123	133	108.1

* Publication date.

Age at Onset. Mortality data presented in an earlier paper[3] indicate a characteristic age distribution in diabetes; the death rate, regardless of sex, increases steadily throughout life, reaching a maximum in old age. Since diabetes is a chronic disease, however, the age at onset is much more important than the age at death. Consequently clinical records give a much truer picture of this characteristic of the disease than do mortality records. The time of onset of diabetes, as is well known, is not usually definite, especially in the milder cases occurring in later life, but it can be fixed with reasonable accuracy in most cases.

In searching for the date of onset in this series the date of diagnosis

furnished the starting point in the majority of instances. In many it was necessary to use this date as that of onset, but often the type of onset as described by the patient would be helpful, namely, whether *sudden*—in the course of 24 hours; *rapid*—in the course of a week; *gradual*—during a period of 2 months; or just *indefinite*—over a longer period of time. In the latter instance the time of the development of symptoms would be helpful. When doubt existed it was the rule to choose the shortest probable interval between onset and diagnosis.

In this experience the number of patients increases steadily from infancy to a maximum at ages 50 to 54 (Table 4), except for a slight dip in the late teens. The rise is resumed in the late twenties and increases rapidly until middle life. The incidence drops off rather sharply from the peak as old age is approached. Relatively few cases are recorded as having their onset in the eighties and none has been found with onset after age 85.

TABLE 4.—AGE AT ONSET OF DIABETES. PER CENT DISTRIBUTION OF CASES WITH KNOWN AGE AT ONSET. BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Age at onset	Males.	Females.
All ages	100.0	100.0
Under 5	2.1	1.6
5–9	2.9	2.8
10–14	3.8	3.5
15–19	3.3	2.6
20–24	4.0	2.4
25–29	5.3	4.2
30–34	6.6	4.4
35–39	8.1	6.8
40–44	10.3	9.7
45–49	12.7	14.3
50–54	14.4	15.7
55–59	10.7	13.6
60–64	8.7	9.2
65–69	3.8	5.8
70–74	2.2	2.1
75–79	0.9	1.0
80–84	0.2	0.2
85–89	.....	0.1
Median age (years)	46.4	49.2
Number of cases	3,119	3,229

At the younger ages, the number of cases is approximately equal for both sexes. Indeed, at most ages up to 45 the males outnumber the females. Beginning with 45, however, the order is reversed and the number of females is much larger than that of males up to age 70. In old age the numbers are again approximately the same.

The age distribution at onset (Table 5) has changed perceptibly. There has been a definite increase in recent years in the proportion

of patients at the older ages, past 60 among males and past 50 among females. The median age at onset has increased, between 1897 to 1914 and 1925 to 1928, 2 years among males and 4 years among females. These changes, to some extent, reflect the declining proportion of younger persons and the increasing proportion of older persons in the general population. It will be noted that in the period 1915 to 1919 the proportion of males with onset in the third and fourth decades of life is relatively large. This is probably a by-product of the examination of men in these age groups for the draft in the World War.

The point of maximum onset for age (Table 5) has shown little change. Among males this point has shifted between the fifth and sixth decades, but among the latest cases is definitely in the sixth decade. Among females the maximum onset has been in the sixth decade of every period except 1915 to 1919 and has been increasingly well defined.

TABLE 5.—AGE AT ONSET OF DIABETES. PER CENT DISTRIBUTION OF CASES WITH KNOWN AGES. BY SEX AND CALENDAR YEAR PERIODS. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Sex; age at onset.	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.
MALES:					
Under 10	5.0	3.8	6.0	5.0	5.0
10–19	7.1	8.0	5.3	8.7	5.9
20–29	9.3	8.3	12.7	10.5	7.3
30–39	14.7	14.9	17.8	13.5	14.6
40–49	23.1	25.5	25.0	24.0	20.7
50–59	25.1	26.3	23.4	23.4	27.1
60–69	12.5	10.1	7.8	12.7	14.8
70–79	3.0	3.1	2.0	1.9	4.4
80–89	0.2	...	...	0.3	0.2
Median age (years)	46.4	46.4	43.4	45.8	48.4
Number of cases	3,119	424	449	1,033	1,213
FEMALES:					
Under 10	4.4	6.4	5.2	4.3	3.8
10–19	6.1	6.1	10.3	4.3	6.5
20–29	6.5	11.1	7.8	7.0	4.9
30–39	11.2	14.5	12.9	10.9	10.3
40–49	24.1	21.9	25.6	25.3	23.2
50–59	29.2	24.9	24.4	30.8	30.3
60–69	15.1	12.1	10.9	14.3	17.2
70–79	3.2	3.0	2.3	3.0	3.5
80–89	0.2	...	0.6	0.1	0.3
Median age (years)	49.2	46.4	45.9	49.4	50.4
Number of cases	3,229	297	348	1,128	1,456

Certain anomalies in the sex and age distribution, particularly among females, are also brought out by the table. Among males, when the experience is divided up into the several calendar periods, the number of cases increases with age up to the maximum in every

period with but a single exception, which can be dismissed as a chance phenomenon due to the small numbers involved. Among females, however, since 1925, the number of patients with onset in the third decade of life has been definitely lower than in the second decade. The reason for this is unknown, but perhaps may be explained on the basis of a preponderance of diabetic children in this series.

TABLE 6.—AGE AND SEX INCIDENCE OF ONSET OF DIABETES. PER CENT DISTRIBUTION OF CASES WITH KNOWN AGES. RECENT CLINICAL EXPERIENCES.

Sex; age groups	Joslin (Boston), 1925–1928.	Cammidge[5] (London), 1934 §	John[7] (Cleveland), 1921–1927.	Mayo Clinic. Wilder[9] 1931–1934	Mayo Clinic. Adams[10] 1926§	Palmer[11] (Seattle), 1919–1934.	Wendt and Peck[13] (Detroit), 1919–1929.	Barach[4] (Pittsburgh), 1925–1935.*	Rabinowitch[18] (Montreal), 1921–1927.† Total persons.	Sevringhaus[12] (Milwaukee), 1922–1930.† Total persons.
MALES:										
0–9	5.0	4.7	1.8	3.7	3.2	7.5	3.2	2.3	2.3	3.6
10–19	5.9	6.4	3.1	5.5	6.7	6.9	6.6	5.3	5.5	12.4
20–29	7.3	11.9	5.3	5.8	11.1	6.6	8.4	9.8	6.8	8.0
30–39	14.6	15.9	13.0	12.5	14.2	9.9	18.5	23.1	17.9	10.2
40–49	20.7	27.7	21.8	23.2	17.5	24.4	19.8	24.2	27.5	14.8
50–59	27.1	21.9	26.7	27.8	25.9	23.7	19.3	20.1	25.2	22.0
60–69	14.8	11.5‡	28.3‡	17.4	18.4	14.4	20.2	13.3	11.8	21.4
70–79	4.4	...	...	3.8	2.9	6.3	3.7	1.9	2.7	7.6
80 and over	0.2	...	...	0.3	...	0.3	0.3	...	0.3	...
FEMALES:										
0–9	3.8	4.7	1.4	4.7	5.5	4.5	0.4	1.6		
10–19	6.5	6.7	2.3	4.2	5.4	5.5	3.7	3.7		
20–29	4.9	10.2	6.2	5.2	7.5	7.1	5.3	5.0		
30–39	10.3	17.7	11.4	12.3	9.9	7.1	13.5	15.3		
40–49	23.2	19.2	24.7	25.4	22.1	23.2	24.9	35.7		
50–59	30.3	24.6	28.9	32.0	29.3	31.3	31.2	25.9		
60–69	17.2	16.9‡	25.1‡	13.8	18.2	17.6	18.3	11.2		
70–79	3.5	...	...	2.4	1.8	3.7	2.7	1.6		
80 and over	0.3	...	...	...	0.2	...	...	...		
NUMBER OF CASES:										
Males	1,213	598	928	1,248	571	333	379	264	1,316	500
Females	1,456	402	1,058	958	429	380	694	321		

* Age at diagnosis.
† Age at admission to hospital.
‡ 60 and over.
§ Publication date.

Comparison of Age at Onset With Other Experiences. The age and sex phenomena in this experience, with the exceptions noted, are believed to be fairly typical. Comparison with other experiences (Table 6) tends, in general, to confirm this observation. It is readily appreciated, however, that such comparisons must be made cautiously because of the subjective element in the determination of onset. One of the advantages of the present experience is that this element is practically constant throughout the 30 odd years, because the senior author made the diagnosis in all cases and fixed the date of onset in most cases, and even in recent years, as a rule, has checked this date. In some of the other experiences, the age data do not always relate to the date of onset, but sometimes to the date of the original diagnosis or of hospital admission, regardless of previous

treatment. In some cases the facts are not shown separately for each sex—a serious omission as there is a fundamental difference in the onset curves of the two sexes. Good material on the age at onset of diabetes is scarce, and it is hoped that this report will stimulate improvement in this regard.

In general, the several experiences (Table 6) agree in the rapid increase with age in the frequency of onset of diabetes. But the maximum is not always the same, nor is it always well defined. In practically all the experiences, the number of onsets at the very old ages is small. The major differences between the several experiences are probably due either to differences in the method of computing onset or in the type of experience. In the hospital experiences, children tend to be relatively numerous, probably because they form a disproportionately large number of the acute cases, especially coma, which receive hospital treatment.

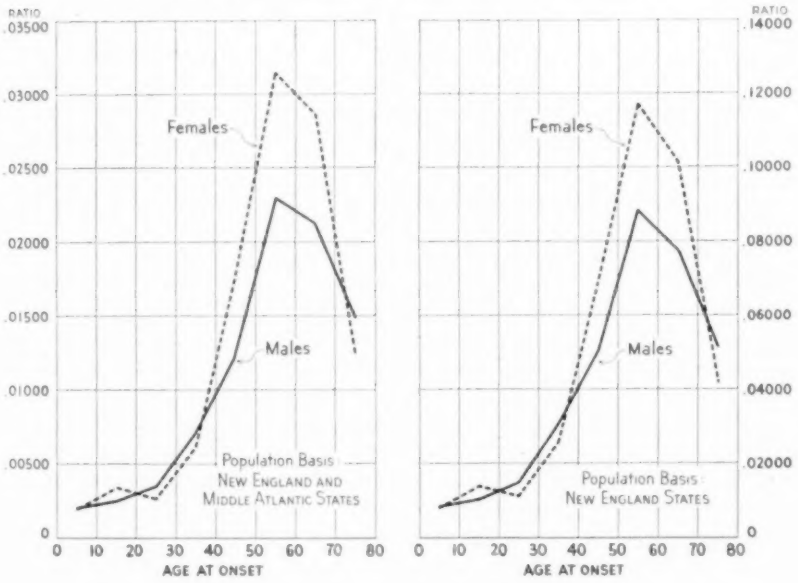
Age Specific Onset Rates. These data on the age distributions at onset in clinical experiences, while adequate as to the numerical frequency according to age, do not represent the rate of onset at each age. For example, the small number of cases at the later ages obviously reflects, to some extent at least, the relatively small proportion of persons at those ages in the general population. The determination of true onset rates according to age is, however, practically impossible, for this would require knowledge of the age at onset by sex for a specific calendar period in a population, the composition of which was known. Obviously, such data are not available and recourse must be made to other modes of analysis.

An original approach to the problem is the estimate by Pincus, Joslin and White[15] of the true proportional age frequencies at onset. Their method consists essentially in weighting the observed frequency of onset in Joslin's experience according to the reciprocals of the proportions surviving to each age of the life table (1_x). While their method gives a better idea of the true profile of the onset curve than the crude figures, it does not permit proper comparison between the relative onset rates of the two sexes, and the life table basis gives undue weight to the older ages.

A more accurate picture is obtained simply by comparing the actual age distribution of the patients in this experience with that of the population from which they are drawn. This has been done by computing ratios of patients to population by age groups. The patients included are those discharged between 1925 and 1928. The analysis was limited to patients seen in this period partly in order to get a more current picture of the situation, and partly because this group is more truly, though by no means entirely representative of the diabetic population than is the entire experience. Two population bases are used, namely, the estimated white population in 1925 of the New England and Middle Atlantic States combined, from which over 90% of the patients came, and the

corresponding population for the New England States only, from which 85% of the patients came. The year 1925 was chosen as an approximate mean year of onset of diabetes in this patient group. This is, strictly speaking, not accurate, but sufficiently close to give trustworthy results. Similar ratios have been computed on the basis of the per cent distribution of the two populations. The derived figures are not true onset rates, but the age relationships are fairly accurate. At the younger ages, they are probably too high, and, after 40, the female curve is certainly too low.

CHART II.—AGE RELATIONSHIPS IN THE ONSET OF DIABETES. RATIO OF PATIENTS OF E. P. JOSLIN, 1925–1928, TO POPULATION OF (*a*) NEW ENGLAND AND MIDDLE ATLANTIC STATES COMBINED AND (*b*) NEW ENGLAND STATES ONLY, JULY 1, 1925 (ESTIMATED). BY SEX AND AGE.



Similar age contours are obtained by all methods. Chart II shows the results based on the ratios of the age distributions. In both sexes the onset rates are lowest in the first decade of life, but rise at first gradually, then very rapidly to a maximum in the fifties, drop off slowly in the next decade, and then rapidly to the end of life. The number of cases recorded in the eighties is too small to show accurately the slope of the curve and the figures, therefore, are omitted from the chart. No onset has been observed in the nineties in this experience; such cases are rare, if they exist at all. Among females there is a definite depression in the curve in the twenties.

When the curves for each sex are compared, it is found that up

to the age of 40 the frequency of onset in males is generally somewhat higher than in females, but from 40 to 70 the frequency of onset in females is appreciably in excess of that for males. During this period of life, when the onset of diabetes is most frequent, the females show a rate of onset approximately one-third in excess of that of males. In the eighth decade, the frequency, based on this experience, seems to be somewhat greater among males, but this is questionable in view of the opposite trend in mortality. The number of cases past 80 is too small to permit a reliable comparison. As we have indicated earlier, the onset curve for females from age 40 on is too low, and the differences between the two sexes, therefore, are actually greater than here shown.

TABLE 7.—INCIDENCE OF JEWISH CASES AMONG DIABETICS. NUMBER AND PROPORTION OF CASES IN SPECIFIED AGE GROUPS. BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Age at onset	Number.		Ratio of Jews to all cases.		Per cent of all ages.	
	Males.	Females.	Males.	Females.	Males.	Females.
All ages	361	528	11.6	16.3	100.0	100.0
Under 5	4	4	6.1	7.8	1.1	0.8
5–9	2	12	2.2	13.2	0.6	2.3
10–14	6	14	5.1	12.5	1.7	2.7
15–19	8	10	7.8	11.8	2.2	1.9
20–24	15	11	12.0	14.3	4.2	2.1
25–29	18	17	11.0	12.7	5.0	3.2
30–34	32	32	15.6	22.5	8.9	6.1
35–39	48	53	18.9	24.2	13.3	10.0
40–44	59	70	18.3	22.3	16.2	13.3
45–49	54	101	13.6	21.8	14.9	19.0
50–54	56	101	12.4	19.9	15.4	19.0
55–59	32	61	9.5	13.9	8.9	11.6
60–64	19	26	7.0	8.7	5.3	4.9
65–69	6	13	5.1	7.0	1.7	2.5
70–74	2	2	2.9	2.9	0.6	0.4
75–79	...	1	...	3.0	...	0.2
Median age (years)	44.1	47.0				

Age at Onset in Jewish Patients. Among Jewish patients in this experience, the onset picture is somewhat different from that of other patients. The Jewish patients developed diabetes relatively early. As Table 7 shows, the maximum numerical frequency of onset of diabetes in Jewish males was between 40 and 44, compared with 50 and 54 for all male patients. In Jewish female patients, equal numbers of onsets were recorded in age periods 45 to 49 and 50 to 54, whereas among all female patients the onset peak was definitely at ages 50 to 54. The median age at onset of the Jewish patients was slightly over 2 years less than that of all patients.

Certain other features of the Jewish experience in regard to sex and age are significant. The number of Jewish female patients exceeded that of males up to the end of 1928 by 46.3%, whereas among non-Jewish patients the number of males was actually slightly greater than females. Considered by age, the number of Jewish female patients was far in excess of the males except in the twenties and thirties. In the late forties and in the fifties, the female cases outnumbered the males nearly 2 to 1.

The proportion of Jewish to total patients (Table 7) varied widely by sex and by age. For all ages, Jewish males constituted 11.6% of all male patients, but females, 16.3% of all female patients. Among males, the proportion of Jewish patients to total patients is relatively small at the younger ages of onset, but increases fairly steadily by age up to the maximum of 18.9% in the late thirties and declines steadily thereafter. Among females, the proportion of Jewish patients is larger at every age than among males. Even at the younger ages at onset, the proportion of Jewish females is well over 10% and increases to a maximum of 24.2% in the late thirties. It then declines, at first gradually, and then somewhat more rapidly with advancing age.

This wide difference in the proportion of Jewish patients at the several ages is certainly not due to chance.[17] It reflects, in some measure, merely the percentage of Jews who, in middle life, are better able to afford and seek expert treatment. This, however, can at best be a partial explanation. We believe that the facts on the age at onset of diabetes in Jewish patients fits in with the mortality data given in an earlier paper,[17] which showed that at the younger ages there is little difference in the diabetes death rates of Jews and non-Jews and only past 45 are the Jewish rates excessive. As for the sharp decline in the proportion of Jewish patients at the older ages, it is, in part, due to the fact that the Jewish population, largely an immigrant one, is deficient in the proportion of old people, but even with reasonable allowance for this it seems that Jewish patients are prone to diabetes in early middle life.

Marital Condition in Relation to Diabetes. The incidence of diabetes is higher in married women than in single women. This difference is not found in men. Indeed, only among the married is there a large difference between the sexes in regard to the frequency of diabetes. This was shown by Mosenthal and Bolduan,[18] from New York City mortality data, and is confirmed by similar Canadian data[19] in the period from 1928 to 1932 (Table 8). The significance of the large difference between married and single women in the Canadian experience between ages 25 and 44 is uncertain, because the average age of the single, in this broad age group, is much lower than that of the married. Unfortunately, more detailed data needed to clear up this point are not available. The widowed have higher rates than the married within the broad

age groups studied, but this also reflects in large part their higher average age.

TABLE 8.—DIABETES AND MARITAL STATUS.[19]
Death Rates per 100,000 From Diabetes. By Sex and Age. Canada, 1928–1932.

Marital status.	Ages 25 to 44.		Ages 45 to 64.		Ages 65 and over.	
	Males.	Females.	Males.	Females.	Males.	Females.
Single	4 3	2 2	21 9	19 2	78 2	71 7
Married	3 2	3 9	18 1	33 1	79 3	138 0
Widowed	*	*	30 5	42 8	97 3	127 0

* Not significant because of small number of deaths.

Partial confirmation of the findings regarding the higher frequency of diabetes in married women is afforded also by analysis of the facts on the marital condition of the senior author's group of patients. These have been tabulated as of the date of examination and compared with the marital distribution of the population of New England in 1920, that year being taken as an approximate mean. On this basis, there was a sizeable deficiency from ages 45 on in the proportion of single persons in this diabetic group, as compared with the general population, both among men and women, but more especially among women. At ages under 45, this relationship did not exist, for the proportion of single persons was higher among the diabetics at ages 20 to 24, and among women not greatly different at ages 25 to 44. This is not altogether surprising. To some extent, this is explained partly by the hesitation of young diabetics to marry, but to a far greater extent by the relatively large number of persons in this diabetic group from families in comfortable circumstances, where marriage tends to be delayed.

Mosenthal and Bolduan[18] suggest that the effect of pregnancy on the carbohydrate tolerance is a factor in the higher incidence of diabetes in married women. This accounts, however, for only part of the difference because diabetes even in married women usually has its onset many years after childbearing has ceased. More important than pregnancy itself would seem to be the effect of overfeeding and underexercise during and after pregnancy. Women usually gain weight during this period, some a considerable amount, and all or a large part of the added weight is often retained. Some indication of this is found in comparing the weights of single and married diabetic women. Among 1326 married women in this group[20] with onset of diabetes after 45, the average weight was 181 pounds, compared to only 161 pounds for 111 single women. No difference, however, was found in the average weights of childless and fertile married women. Another factor in the difference between

the single and married women is the generally better economic status of the married. That means more frequent overnutrition and a greater probability of acquiring diabetes as indicated by the weight figures just quoted. It also means more medical care and a greater probability of correct diagnosis of the disease when it occurs. Moreover, there is greater incentive for a single woman to keep her figure than a married woman. Finally, among single women there is a sizeable proportion who do not marry for reasons of health, most of whom are victims of wasting diseases, and, therefore, underweight.

As for the difference in the frequency of diabetes between married men and women, the extremely rapid increase in the frequency of onset among women in the late forties or fifties reflects the strain on the endocrine system during menopause. Gain in weight is very frequent at this period of life.

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THE "GORDON TEST" FOR HODGKIN'S DISEASE.

By Jacob D. Goldstein, M.D.,

INSTRUCTOR IN MEDICINE, UNIVERSITY OF ROCHESTER, SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, N. Y.

(From the Departments of Medicine and Bacteriology.)

In 1932–33 Gordon[1] reported that an encephalitic syndrome of characteristic pattern developed in rabbits injected intracerebrally with suspensions of lymph glands removed from patients with Hodgkin's disease. He obtained this reaction from 19 of the 20

lymphadenoma cases which he studied. Gland biopsies from 41 patients suffering from a variety of conditions (carcinoma, lymphosarcoma, leukemia, tuberculosis) did not produce this effect in rabbits. Van Rooyen[2] similarly studied 20 cases of Hodgkin's disease. Fifteen of these glands produced a picture of encephalitis in rabbits, whereas 13 non-lymphadenomatous glands were negative.

The nature of the agent responsible for this reaction has not been definitely established. Gordon[1] has suggested that a virus may be involved. Van Rooyen,[2] however, considered the response to be a toxic phenomenon, and felt that the absence of demonstrable immunity, the absence of intracellular inclusions, and the inability to transmit the encephalitis from rabbit to rabbit, constituted strong evidence against any virus as an etiologic agent. Friedemann[3] has shown further that the intracerebral injection of normal splenic tissue, of bone marrow (normal or pathologic) or of normal leukocytes (all from humans) produced in rabbits an encephalitis similar to that described by Gordon after inoculation with lymphadenomatous tissue. He suggested that the encephalitogenic agent in Hodgkin's glands, in normal spleen, in bone marrow and in leukocytes was of the nature of a proteolytic enzyme. A proteolytic enzyme was demonstrated in human spleen, bone marrow and leukocytes by Jochmann and Lochemann[4] in 1908.

The problem of the identity of the Jochmann-Lochemann proteolytic ferment with the encephalitogenic agent found in Hodgkin's disease has been studied further by MacKenzie and Van Rooyen.[5] Their results indicate that there is no relationship between the proteolytic and the encephalitogenic properties of a given gland extract. Experiments directed at this phase of the problem are in progress in this laboratory now and will be discussed in a later communication.

In the reports of Gordon and of Van Rooyen, only Hodgkin's lymph nodes produced an encephalitis in rabbits. Lymph nodes from other diseases did not produce this reaction, although in several instances lymphadenomatous nodes failed to produce it. These reports indicated that the injection of suspensions of Hodgkin's lymph nodes into rabbit brains might serve as a valuable biologic test for the presence of Hodgkin's disease. Manson,[6] however, reports 3 false positive tests; in 2 instances from nodes histologically diagnosed tuberculosis and in 1 node showing simple hyperplasia.

The purpose of this report is to present our experience with the "Gordon test."

Method and Material. *Method.* Lymph nodes obtained by biopsy were sent to the laboratory immediately after removal from the patient. Using sterile technique, the gland was weighed, after as much as possible of the fatty and fibrous tissue had been dissected away. It was then minced with scissors in a mortar, and thoroughly ground up with a pestle. Enough broth was then added to make a

10% suspension. The broth used (both in grinding and diluting) contained 0.5% phenol and its reaction was accurately adjusted to a pH of 7.1.

The gland suspensions were tested for sterility after grinding, and always on the day preceding and on the day of injection into animals. All emulsions were kept in cotton-stoppered tubes in the icebox at 6° C. and injected into animals after from 8 to 10 days of storage. Where the material was adequate in amount, injections into rabbit brains were made 24 hours after preparation of the suspensions. When the results were negative, further inoculations were made in from 15 to 20 days, and in several instances after a longer period of storage.

The rabbits were injected in the manner suggested by Gordon. Under light ether anesthesia, 0.25 cc. of gland suspension was given intracerebrally and from 0.5 to 0.75 cc. intravenously. The animals were examined daily. Temperatures and weights were recorded daily at first. Later the temperature was taken only when the animal showed abnormal signs, and the weights were recorded intermittently as the animals' clinical status changed.

Only definite neurologic changes, such as spasticity, ataxia, tonic fits on stimulation, and delayed flaccid paralysis were accepted as criteria of a positive test. Hyperexcitability and tremor in the first 72 hours after injection were not considered to be significant. At first the animals were observed for 21 days, but later this period was extended to from 30 to 35 days.

Material. Twenty-nine lymph nodes have been studied. Nine came from patients with Hodgkin's disease, as proved by histologic study. The other 20 biopsy specimens were from patients clinically suspected of having Hodgkin's disease, but the histologic examinations did not show Hodgkin's granuloma. A résumé of the individual cases of Hodgkin's disease, including the results of the rabbit tests, follows:

Case 1. E. V., female, aged 34, was admitted June 7, 1934, for a dermatitis of unknown etiology. She returned 2 months later with swollen cervical glands; leukocytes, 23,600. Biopsy of gland showed histologically typical Hodgkin's granuloma.

Rabbits 103 and 104 were inoculated with a suspension of excised gland which had been stored in the icebox for 9 days. Both animals showed neurologic changes on the 5th or 6th day. Progressive ataxia, spasticity and cachexia developed. Animals killed after a month for histologic study.

Case 2. M. B., male, aged 48, was admitted November 1, 1934, because of intense abdominal pain of 3 weeks' duration. The significant findings were generalized glandular enlargement, enlarged liver and spleen, and anemia. Biopsy of axillary gland showed histologically typical Hodgkin's disease.

Rabbits 142, 666, 826 and 828 were inoculated with gland suspension stored in the icebox for 3 days. All 4 animals developed signs of an encephalitis.

Case 3. E. N., female, aged 70, was admitted November 21, 1934, because of weakness of 5 months' duration. A small mass was found in

the left axilla. Biopsy of this mass showed histologically typical Hodgkin's disease.

Rabbits 145 and 146 were inoculated with gland suspension stored in the icebox for 11 days. These animals remained normal. Rabbits 901 and 902 were inoculated with node suspension stored in the icebox for 27 days. Both animals developed encephalitic symptoms characterized by spasticity, ataxia and spastic fits. Both died.

CASE 4. R. B., female, aged 26, for 2 years had swollen glands in the neck. Biopsy during March, 1934, did not establish a diagnosis. The biopsy wound drained for 3 months. In January, 1935, generalized lymphatic enlargement developed. Biopsy of axillary node revealed a histologic picture of which Dr. G. H. Whipple said: "Definitely Hodgkin's disease—but tuberculosis might be present."

Rabbits 162 and 163 were inoculated with node suspension stored in the icebox for 7 days. Both animals developed typical signs of encephalitis on the 4th day. Four guinea pigs inoculated with fresh and stored node material did not show any tuberculosis on autopsy. The guinea pigs were also given skin tests with tuberculin. The reactions were negative.

CASE 5. J. C., male, aged 60, with no reliable history. Material was obtained at autopsy on October 28, 1934. Involved lymph-nodes were obtained from neck, axillæ, and retroperitoneal regions. The spleen, liver and lungs were also involved. All were histologically typical of Hodgkin's disease. Lymphatic tissue and infiltrated tissue from liver and spleen were prepared and stored in the icebox for 17 days. One rabbit was inoculated with suspension from each tissue. All rabbits developed typical signs of encephalitis during the 4th, 5th and 6th days.

CASE 6. P. C., male, aged 7, admitted March 23, 1935, was first seen on May 8, 1930, when a generalized enlargement of lymph-nodes was noted. Biopsy of an inguinal gland was performed on August 1, 1930. Histologically, a diagnosis of subacute lymphadenitis was made with Hodgkin's disease listed as a possibility (Dr. G. H. Whipple). A second biopsy on November 14, 1931, showed a histologic appearance more closely resembling that of Hodgkin's disease. Biopsy on March 27, 1935, demonstrated an appearance histologically typical of Hodgkin's disease.

Rabbits 741 and 744 were inoculated with lymph-node suspension stored in the icebox for 10 days. Both rabbits developed symptoms of encephalitis on the 4th day.

CASE 7. T. M., male, aged 26, for 6 months had intense itching of both wrists; for 2 months, increasing swellings in the neck. Diffuse enlargement of lymph nodes was observed. Biopsy showed typical Hodgkin's lymphogranuloma.

Rabbits 790 and NL were inoculated with node suspension which had been stored in the icebox for 16 days. Both animals developed abnormal neurologic signs on the 5th day.

CASE 8. G. G., male, aged 62, admitted on June 2, 1933, for respiratory difficulty. Widening of mediastinal dullness and a generalized lymphadenopathy were present. Biopsy of an axillary gland on September 6, 1933, demonstrated typical Hodgkin's granuloma. A second biopsy on October 27, 1933, also showed Hodgkin's granuloma. Death occurred on November 21, 1933. At autopsy, lesions entirely typical of Hodgkin's disease were found in liver, spleen, kidneys, skin and lymph-nodes.

Nine rabbits were inoculated with material obtained at both biopsies and at autopsy. Dosage and duration of icebox storage were varied. All tests, however, were entirely negative.

CASE 9. J. H., male, aged 39, had enlargement of cervical lymph-nodes, noted in May, 1934. There occurred progressive development of a diffuse lymphadenopathy with intermittent fever. Biopsy on October 9,

1933, showed histologically typical Hodgkin's granuloma. The patient died during February, 1935. The gross and histologic findings at autopsy substantiated the diagnosis of Hodgkin's disease.

Rabbits 641 and 642 were inoculated with lymph-node suspension stored in the icebox for 11 days. Both animals remained normal. Rabbits 643 and 644 received the same suspension after storage in the icebox for 20 days. Both animals remained normal. Material prepared from autopsy specimens also gave negative results on inoculation into 11 rabbits.

Control Material. The biopsy specimens from 20 patients did not show histologic evidence of Hodgkin's granuloma. These node suspensions did not produce neurologic changes in any of the animals injected. A summary of these cases is given in Table 1.

TABLE 1.—CONTROL GROUP.

Patient.		Sex.	Age, yrs.	Clinical diagnosis.	Histologic diagnosis.	Source of gland.	Gordon test.
W. B.	73658	M	41	Pulmonary tuberculosis	Tuberculosis	Axilla	Negative
M. O.	86948	F	30	Glomerulonephritis	Chronic lymphadenitis	Neck	"
E. W.	95140	F	34	Not determined	Chronic lymphadenitis with cystic changes	Mesentery	"
A. G.	87860	M	17	Tuberculous adenitis	Hyperplastic tuberculosis	Neck	"
F. S.	96533	M	61	Lymphatic leukemia	Lymphatic leukemia	Neck	"
C. A.	70606	M	23	Infectious mononucleosis	Chronic lymphadenitis	Neck	"
R. F.	65568	M	21	Infectious mononucleosis	Chronic lymphadenitis	Axilla	"
L. P.	90188	M	20	Chronic nephritis	Hyperplastic node	Neck	"
M. M.	81335	F	33	Tuberculous adenitis	Tuberculosis	Neck	"
B. D.	21540	M	8	Tuberculous adenitis?	Chronic lymphadenitis	Neck	"
V. T.	(HH)	F	33	Ulcerative colitis	Chronic lymphadenitis	Mesentery	"
Y.	(AOH)	M	25?	Leukemia	Leukemia	Neck	"
P. T.	95426	F	22	Banti syndrome?	Hyperplastic node	Axilla	"
W. M.	100968	M	26	Lymphosarcoma	Lymphosarcoma	Axilla	"
L. C.	99987	F	34	Tuberculous adenitis	Tuberculosis	Neck	"
D. V.	869	M	36	Lues? Tuberculosis?	Hyperplastic node	Axilla	"
C. Z.	1191	F	27	Lymphosarcoma	Lymphosarcoma	Groin	"
A. S.	A2888	M	65	Cardiac death	Lymphosarcoma	Retroperitoneum (autopsy)	"
G. D.	(RGH)	F	47	Profound anemia—Cause?	Tuberculosis	Neck	"
C. N.	100778	M	15	Not determined	Hyperplastic node	Neck	"

Discussion. Seven of 9 lymphogranulomatous nodes, when inoculated intracerebrally into rabbits, produced an encephalitic syndrome. In 2 instances, where tissue was obtained from histologically established cases of Hodgkin's disease, this reaction was not obtained. From both, biopsy specimens were obtained on 2 occasions, and enough material was available at autopsy to permit making an adequate number of rabbit tests. Dosage and time of icebox storage of the suspensions varied, but all of the inoculated animals remained free of abnormal neurologic manifestations.

Of the control group of 20 lymph nodes, 5 were tuberculous and 2 came from patients with infectious mononucleosis. None of the control glands produced signs of encephalitis on inoculation into rabbits.

The results of our limited series of observations suggest that the "Gordon test" may be of distinct value in the diagnosis of Hodgkin's disease, especially in those instances where the histologic findings are uncertain. A negative test at the present time has no diag-

nostic significance. It is apparent, however, that in order to settle the question of possible "false positive tests," additional cases must be studied.

Summary. 1. Biopsy material from 7 of 9 cases of Hodgkin's disease produced an encephalitic syndrome (a positive "Gordon test") when inoculated intracerebrally into rabbits.

2. Twenty control lymph-nodes, including 5 tuberculous nodes and 2 nodes from infectious mononucleosis were negative.

3. There were no false positive tests. Two of 9 nodes from established cases of Hodgkin's disease failed to give a positive test.

The author wishes to express his thanks to Dr. G. P. Berry and Dr. J. S. Lawrence for interest and help in this work.

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HODGKIN'S DISEASE OF THE LUNG.*

By Ernest H. Falconer, M.D.,
CLINICAL PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
AND
Maurice E. Leonard, M.D.,
ASSISTANT IN MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
SAN FRANCISCO, CALIF.

(From the Departments of Medicine and Pathology, University of California Medical School, San Francisco, Calif.)

The material for this report was obtained from a study of 29 patients with a diagnosis of Hodgkin's disease who were admitted to the University of California Hospital from 1928 to 1935. It is our purpose to describe, from our analysis of this material, the clinical, roentgenologic and pathologic manifestations of pulmonary involvement in Hodgkin's disease. We have used data from published reports in the literature for comparison and amplification of our data. Of the 29 cases studied, 9 showed clinical or pathologic

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evidence of pulmonary involvement. Seven of these cases are reported in essential detail.

Incidence. Our search of the literature has revealed the following published statistics of incidence (Table 1). These series are all small, probably on account of rigid diagnostic criteria, including autopsy. Our series appears larger by reason of less rigid criteria, as not all of the patients came to autopsy. The diagnosis in every instance of our 29 cases, however, was carefully checked by biopsy material and histologic study. Although the total number of reported cases is small, and despite the different diagnostic criteria used (clinical or pathologic), it will be noted that the reported statistics agree closely.

TABLE 1.

Author.	Total number cases.	With pulmonary involvement.	Per cent.
Ceelen-Rabinowitsch	10	4	40 0
Herxheimer	8	5	61 0
Sternberg	15	5	33 3
Weinberg	7	2	28 0
Versé	16	6	37 0
Moolten	18	9	50 0
Whitaker	22	7	32 0
Authors	29	9	31 0
Total	125	47	37 6

The report of 7 authors show the incidence of pulmonary involvement to be 40%.

Pathology. The lesion may be primary or secondary. The primary type is very rare, although Moolten[1] includes it in 10% of all cases of pulmonary Hodgkin's disease. The primary forms arise from lymphoid nodules within the lung parenchyma and the submucosa of the bronchi, the so-called submucosal and auxiliary lymphoid tissue.[2] The secondary type most commonly invades the lungs from the bronchomediastinal lymph nodes, but may extend from the thoracic spine, ribs, pleura, pericardium or thymus. Bernard[3] states that a primary origin in the pleura is more common than in the lung.

Versé[4] classifies pulmonary Hodgkin's lesions as follows:

1. Hilus node involvement with direct invasion of lung tissue: (*a*) By direct extension from the lung hilus; (*b*) by breaking through the mediastinal pleura.
2. Hilus node involvement with intra- and peribronchial spread into the lungs.
3. More or less lobar infiltration with various grades of bronchomediastinal involvement.
4. Confluent lobular foci with associated involvement of lymph nodes.
5. Miliary disseminations.

Grossly, the lesions may resemble metastatic tumor nodules,

massive expansive growths, lobar consolidation or miliary dissseminations; and numerous cases with cavity formation have been reported.[5–10] Lyon[11] reported a case in which the granuloma had perforated the chest wall.

Histologically, one may find typical granulomatous tissue invading and following peribronchial and perivascular structures, also frequently extending into the interstices and alveoli.

Pleural effusion may occur in association with infiltration of the lung or pleura. Effusion may be due to mechanical factors alone, *i. e.*, pressure upon the great vessels by glandular masses. Serosanguinous, serofibrinous, or even purulent effusions occur, and are usually very cellular. Cases with chylous effusion have been reported. According to Bernard,[3] any effusion which cannot be explained in any other way should lead to suspicion of primary pleural Hodgkin's disease.

Among our patients, using the Versé classification above, we found 1 case corresponding to Type 1, 1 corresponding to Type 5, 2 corresponding to Type 2, 1 each corresponding to Types 3 and 4, and 1 corresponding to a combination of Types 2 and 3.

Symptoms and Signs. The symptoms associated with pulmonary Hodgkin's disease are most frequently cough and dyspnea; less frequently, chest pain, expectoration and hemoptysis. Of 7 patients presented in detail in this report, 6 had dyspnea; 5, cough; and 1, chest pain. Five showed signs of fluid; 2 of these showed signs of consolidation, and 2 showed only scattered râles. Dyspnea of marked degree was a symptom of those patients with extensive pleural effusions, although it was also marked in 3 patients having infiltration of the lung without the presence of fluid. Cough, usually unproductive, occurred in all patients showing parenchymatous lesions. Chest pain was a striking symptom in 1 case. In another patient, cough was the predominant symptom before infiltration of the parenchyma had occurred. Two patients had respiratory symptoms at the onset of the disease. In 1 of these, cough was the symptom first prompting the patient to seek medical advice. In the other 5 patients the respiratory symptoms appeared 5 months, $2\frac{1}{2}$ years, 3 years, 3 years and 9 months, and 8 years after the onset of lesions elsewhere in the body.

Roentgenologic Findings. There is no characteristic Roentgen picture of pulmonary Hodgkin's disease. If the film reveals miliary disseminations, or infiltration or cavitation of the upper lobes, tuberculosis is suggested. If the shadows resemble metastatic nodules or large expanding tumors, carcinoma is suggested and may be the diagnosis made. In 1 of our cases the early Roentgen diagnosis was tuberculosis, while in another it was metastatic carcinoma.

In the majority of cases where there is evidence of Hodgkin's disease elsewhere in the body, the Roentgen findings will establish

the diagnosis of pulmonary involvement. The difficulty in these cases is the possible coëxistence of pulmonary tuberculosis. We have not found this association to be common, either in our own cases or in reports from the literature.

The greatest difficulty presents itself in those cases where the primary lesion is in the lungs. Here tuberculosis, lymphosarcoma, carcinoma, or chronic pneumonitis may give similar pictures. Many roentgenologists believe that tuberculosis and carcinoma can be fairly sharply differentiated from lesions due to Hodgkin's disease. Whitaker[12] lays stress upon the sharper outlines of sarcomatous and carcinomatous lesions. Wessler and Greene[13] stress the enlargement of paratracheal nodes in Hodgkin's infiltration. The response to Roentgen ray treatment may be of help in the differential diagnosis.[14,15,16] Tuberculosis will show no response. Carcinoma responds slowly, if at all. On the other hand, the lesions of Hodgkin's disease and lymphosarcoma should regress rapidly. It is stated by some authors that lymphosarcoma will show a more rapid rate of regression than Hodgkin's lesions, but this depends to a large extent upon the relative degree of cellularity and fibrosis of the lesion. It should be stated that there are investigators who believe that radiation does not cause satisfactory regression of Hodgkin's lesions in lung parenchyma. For this reason the response to radiation may not be of much help as an aid in differential diagnosis.

Prognosis. We were unable to determine any definite connection between the time of onset of the pulmonary symptoms and the time of death (Table 2). This may be due in part to the variable interval between the appearance of the lesion and the onset of symptoms. Moreover, there is no definite relationship between the extent of the lesion and the symptomatology. If pleural effusion occurs early, the symptoms are marked, whereas it has been noted that extensive infiltration of the lung parenchyma may exist without symptoms pointing to the chest.

TABLE 2.

Case No.	Time of appearance of chest symptoms after onset of disease.	Length of life after onset of pulmonary involvement.
1	2 years, 6 months	2 months.
2	5 months	Subsequent course not known.
3	8 years	2 years, 3 months.
4	Primary symptoms	4 years, 3 months.
5	3 years	3 months.
6	3 years, 9 months	1 year, 9 months.
7	With onset of disease	1 year, 4 months.

Case Reports. CASE 1.—M. W., male, aged 22, entered the hospital May 5, 1933. The chief complaints were weakness, diarrhea, loss of weight and swelling of glands in the neck. Two and a half years prior to entry, following tonsillectomy, he had noted swelling of the left side of the neck. In July, 1931, glands were removed from the neck, followed by

Roentgenotherapy. Progressive weakness and loss of weight supervened with intermittent periods of diarrhea, which lasted until the present entry. Two weeks prior to entry he began to have a non-productive cough. Physical examination showed: Respirations, 35 per minute; occasional sonorous râles in the left interscapular region. For 2 days following admission the patient was very dyspneic. On May 9, the possibility of emphysema was considered. During his stay in the hospital, he suffered from intermittent attacks of dyspnea which could not be accounted for by the chest findings. Occasionally a few râles were heard. The respirations ranged from 30 to 60 a minute. A Roentgen film, taken June 3, showed diffuse parenchymatous shadows throughout the right lung field, and to a lesser extent in the left lung field (Fig. 1). The patient was discharged on June 6. Death occurred in July, 1933. No necropsy.

CASE 2.—R. B., female, aged 37, was admitted, July 17, 1933, with weakness, loss of weight, dyspnea, intermittent fever and swelling in the neck. Her first symptoms appeared in August, 1932, and consisted of left temporal headache, itching of the skin and rash. This condition cleared up and the patient felt well until January, 1933. Following an attack of influenza she complained of dyspnea, a loss of 25 pounds in weight, and intermittent fever. In March, 1933, she noted swelling on the right side of the neck, followed by swelling of the left side of the neck and in the axillæ and groins. She had also noted excessive pigmentation on her body for 2 months. Just prior to admission, dyspnea was the most annoying symptom. Physical examination showed: Brownish pigmentation of the face and arms. Large masses of discrete and confluent, slightly tender glands in the cervical, axillary and inguinal regions. Chest examination showed diminished mobility of the left side; dullness over the left base posteriorly. Breath sounds at the right apex posteriorly were high-pitched and bronchial. Numerous fine, subcrepitant râles were heard throughout. The spleen and liver were palpable. There was pitting edema of both ankles, and fluid in the abdomen. The pupils were fixed and reacted sluggishly to light; knee jerks were diminished. Kahn test, 4+. A roentgenogram of the chest taken, July 18, 1933, showed scattered area of density through both lower lobes and the left upper lobe (Fig. 2). She received five courses of deep Roentgen therapy to the chest. Following irradiation there appeared to be clinical improvement in her chest condition. She was discharged, July 29, 1933, and returned to her physician. Her course since discharge is not known.

LEGENDS FOR FIGS. 1 TO 11.

FIG. 1.—Diffuse parenchymatous involvement of the right lung. Lesser involvement of the left lung.

FIG. 2.—Scattered areas of density through both lower lobes and left upper lobe.

FIG. 3.—Large collection of fluid at right base. Small collection at left base.

FIG. 4.—Perivascular infiltration with lymphogranulomatous lesion extending into lung parenchyma.

FIG. 5.—Diffuse shadows extending throughout both lung fields.

FIG. 6.—Circumscribed nodule of lymphogranulomatous tissue.

FIG. 7.—Fluid level in the left chest extending to the third rib.

FIG. 8.—Large smooth shadow in the region of the left hilus.

FIG. 9.—Mediastinum clear. Infiltrating lesion extending down to base of right lung.

FIG. 10.—Increased peribronchial shadows producing increased linear shadows throughout the left lung field. Density at the right base.

FIG. 11.—Peribronchial infiltration. Marked fibrosis in lower part of field.

FIG. 1

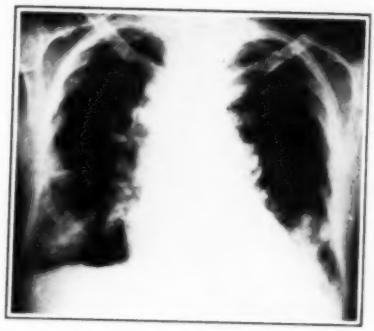

FIG. 2

FIG. 3

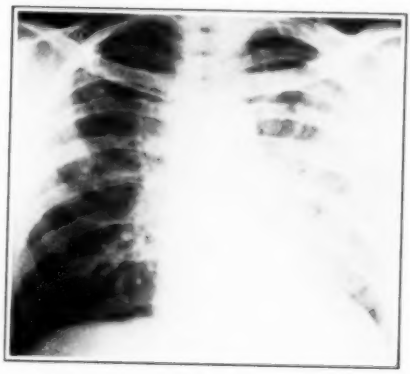

FIG. 5

FIG. 4

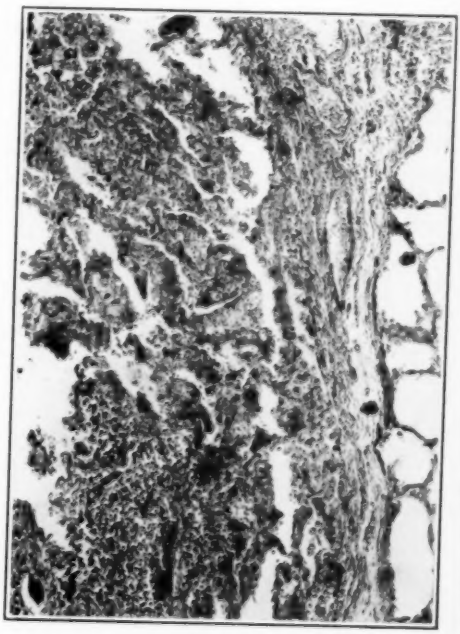

FIG. 6

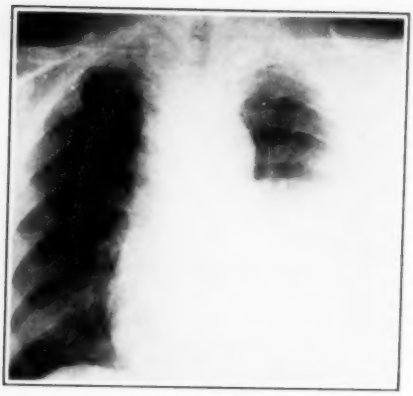

FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 11

CASE 3.—R. F., male, aged 56, was admitted, July 20, 1931, complaining of dyspnea of 2 years' duration. Ten years before, he had noted swelling of the neck. A gland was removed and a histologic diagnosis of Hodgkin's disease was made. In 1927, he had had some Roentgenotherapy. For several years he had nocturnal attacks of orthopnea. Physical examination on admission showed signs of bilateral pleural effusion. Fourteen hundred cc. of clear yellow fluid were removed from both sides. Five days later, 1850 cc. of fluid were removed from the right side. Chest films taken on July 28 showed a large collection of fluid at right base and a small collection on the left (Fig. 3). He received 2 Roentgen ray treatments to the chest, following which there was no improvement in the patient's symptoms. Death occurred on October 9, 1931. At necropsy, the left pleural cavity contained 5000 cc., and the right pleural cavity 4000 cc. of seropurulent fluid. The lungs were normal in weight. There were small, white foci scattered over the pleural surface. No other gross lesions were noted. Microscopic examination of the lungs showed small areas of perivascular cellular infiltration. The cells consisted of lymphocytes, endothelial cells and occasional giant cells. There were no eosinophils. No fibrosis (Fig. 4).

CASE 4.—L. P., male, aged 30, was seen in consultation with Dr. Alexander Bartlett, of San Francisco, by one of us (E. H. F.). In December, 1928, the patient was thought to be suffering from arthritis of the upper spine. In March, 1929, he developed a cough; and a chest plate taken at that time showed enlarged mediastinal shadows. From 1930 to 1931, he received periodical Roentgenotherapy to the chest. He was admitted to the hospital on December 8, 1931. Physical examination showed enlarged glands in the axillæ. There was some impairment of the percussion note and breath sounds over the left side of the chest. A chest film taken, December 11, showed 2 circumscribed, rounded nodules in the left lower lobe. A diagnosis of metastatic carcinoma was made. A course of Roentgenotherapy was given and he was discharged on December 16, 1931. On December 26, he was readmitted, receiving another course of deep Roentgenotherapy. On January 2, 1932, he was discharged with no apparent change in his condition since the first entry. On January 23, 1932, he was again admitted. Between the present and previous entries he had been confined to bed because of severe dyspnea. Three days before admission, 2500 cc. of greenish fluid were removed from the right pleural cavity. On January 26, 1800 cc. of greenish fluid were removed. Culture showed no growth. Pathologic examination of the cellular material from the fluid gave findings consistent with Hodgkin's disease. A chest film taken at this time showed diffuse shadows extending through both lung fields (Fig. 6). On January 28, histologic examination was made of a gland removed from the axilla; the diagnosis was Hodgkin's disease. The patient's dyspnea was so extreme that after repeated tappings the possibility of a bronchial stenosis was entertained. Bronchoscopy, however, showed no obstruction. Death occurred on March 18, 1932. Necropsy showed the right pleural cavity to be filled with blood-stained fluid. The right lung was collapsed and adherent on the anterior and posterior surfaces. It contained scattered areas of nodular consolidation, varying in size from 0.5 to 3 cm. The mediastinum was completely filled with similar nodules. The left pleural cavity contained 800 cc. of clear, yellow fluid. The left lung was studded with firm nodules similar to those seen in the right lung. Microscopic examination showed marked congestion and edema. There were very large circumscribed areas in which the lung architecture was completely lost. Practically no alveolar structure was made out. In some places only a dense hyalinized fibrosis was present. In others, fibrosis was less marked and showed a cellular infiltration, while in still others a cellular infiltrate predominated. The infiltration exhibited marked

pleomorphism and consisted of lymphocytes, endothelial cells, giant cells and occasional eosinophils. The giant cells were mononuclear and multinuclear. In some the nuclei were arranged about the periphery, while in others they had a central arrangement. The nuclei were hyperchromatic. A few mitoses were noted (Fig. 6).

CASE 5.—C. R., male, aged 49, in November, 1931, noted swelling of the neck. In April, 1932, a diagnosis of Hodgkin's disease was made by histologic examination of a gland. A chest film taken, May 19, showed a few dense parenchymatous shadows of small size in the right upper lobe. Between April and July, 1932, he was given 10 Roentgen ray treatments. In August, he was admitted to the hospital complaining of pressure on the throat, interfering with breathing and swallowing. He also complained of sharp pain in the left side of the chest associated with dyspnea, and an unproductive cough which had been present for 3 weeks. Physical examination showed signs of fluid in the left pleural cavity, extending to the level of the third rib (Fig. 7). On August 6, 2000 cc. of clear, yellow fluid were removed from the left pleural cavity. On August 11, a chest film showed widening of the mediastinum above the aorta and peribronchial infiltration in the left lower lobe (Fig. 10). On this admission, cutaneous nodules were found which histologic examination proved to be lesions of Hodgkin's disease. Death occurred on October 6, 1933.

CASE 6.—W. M., male, aged 36, in August, 1928, complained of itching. In January, 1929, examination disclosed a typical urticarial rash and some enlarged lymph nodes in the right supraclavicular region. In February, 1929, a diagnosis of Hodgkin's disease was made from histologic examination of a lymph node. A Roentgen film, taken April 2, 1930, showed a large, smooth shadow in the region of the left hilus (Fig. 8). He had several courses of Roentgenotherapy. In June, 1930, an enlarged gland was found in the left axilla. In September, small, shotty glands appeared in the anterior triangle of the left side of the neck. In April, 1931, he first began to cough. A Roentgen film, taken September 3, showed an infiltrating lesion extending from the right hilus to the base of the right lung (Fig. 9). In November, thoracentesis of the right chest was performed and 1500 cc. of serosanguineous fluid removed. This was repeated several times before death occurred, in January, 1932.

CASE 7.—H. V., male, aged 25, in April, 1933, noted a dull, aching pain across the lower back. At the same time glandular enlargements appeared in the neck, axillæ and groins. This was followed by fever, anorexia, malaise and loss of weight. Since the onset of the illness, he has had dyspnea and productive cough. He was admitted to the hospital on March 1, 1934. Physical examination showed the presence of fluid in both pleural cavities. A Roentgen film taken on March 2 showed increased density in the peribronchial structures leading from the left hilus to the base. Thoracentesis was performed on March 15. A clear, yellow fluid was obtained. A pleural friction rub was heard in the right lower axilla on March 20. On April 10, the patient complained of precordial pain, and a pericardial friction rub was elicited. Five doses of Roentgenotherapy were given over the chest. The patient was discharged on March 4, 1934. He was readmitted, May 29, with nausea and vomiting, marked dyspnea, productive cough and pain across the front of the chest. Physical examination showed signs of fluid at both bases, with displacement of the mediastinum to the right. From May until August, repeated thoracenteses were performed and large amounts of serosanguineous fluid withdrawn. A chest film, taken August 2, 1934, showed increased peribronchial shadows throughout the left lung (Fig. 10). The condition was aggravated by marked abdominal ascites, a failing heart and renal insufficiency. Death occurred on August 25, 1934. Necropsy findings: Pleural cavities were

filled with thin grayish fluid which compressed the lungs until they occupied about one-fourth of the chest cavity. There were a few filmy adhesions at the left apex and at the right base posteriorly. The parietal pleura was studded with white nodular infiltrations. The bronchomediastinal nodes were enlarged, and on cut section showed fibrosis and occasional hyperplastic, glandular areas. Both lungs were markedly compressed. The right weighed 380 gm. and the left 410. There were many small, rounded, yellow nodules in the parenchyma of the left lung, particularly in the bronchial regions. The right lung showed a small area of atelectasis at the base. Microscopic examination showed peribronchial, and to a lesser extent perivascular, fibrosis. These fibrosed areas contained numerous lymphocytes, neutrophils, eosinophils and reticular cells. Occasional Sternberg-Reed cells were found (Fig. 11).

Summary. The conclusions from our studies are in accordance with those of other students of this disease who have been interested in the incidence of pulmonary involvement. If 37.6%, which is an approximate incidence of pulmonary involvement as shown by Table 1, should hold in larger series, then pulmonary Hodgkin's disease is not rare. The ratio of pulmonary involvement to the total number of cases of Hodgkin's disease would actually work out to be relatively high.

Five of the 7 cases showed pleural effusion. This is 71%, which is somewhat higher than one would expect to find in a larger series of cases. Three of these cases with pleural effusion showed pleural lesions, due to Hodgkin's granuloma, at autopsy. We were unable to form an adequate idea, from our small series of patients, of the average tenure of life after pulmonary involvement is definitely ascertained.

We are preparing a report, to follow this study, dealing with pulmonary involvement in patients with lymphosarcoma and leukemia. This should prove interesting from the standpoint of comparison.

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PLASMA CELL LEUKEMIA.

A Consideration of the Literature With the Report of a Case.

By Arthur J. Patek, Jr., M.D.,
Assistant in Medicine, Harvard Medical School; Resident Physician, Thorndike Memorial Laboratory,
and
William B. Castle, M.D.,
Associate Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory, Boston, Mass.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.)

Although more than 400[1] cases of plasmacytoma* have been recorded in the literature, the finding of plasma cells in the peripheral blood in this disease seldom has been mentioned. Aschoff,[2] in 1906, was the first to describe such a condition. Lindh-Muller and McNaughton,[3] in 1931, reviewed 6 reports of plasmacytoma with the blood picture of plasma cell leukemia and added observations on 2 more cases. In 1934[4] Osgood reported such a case, and another has been recorded recently at the Massachusetts General Hospital.[5] Thus, of a total number of 11 cases, 4 have been observed in this community during the past 4 years. Whereas it is a rare condition, we venture to predict that the disease occurs more often than commonly is appreciated. Since it is readily diagnosed when suspected, it has seemed worthwhile reporting an additional case of plasmacytoma with a blood picture of plasma cell leukemia.

* The term plasmacytoma is used to express plasma cell tumors described by the names of plasmoma and multiple myeloma.

Case Report. An American housewife of 60 entered the hospital in December, 1934, complaining of pain in the right chest. Except for chronic constipation she had always been in robust health. During the previous year she had tired easily and had suffered fleeting pains in the back and shoulders. For about 8 weeks she had experienced recurrent pains, first in the right and later in the left chest, which recently had become so sharp and constant that she took to bed. Deep breathing or change of posture in any direction intensified her discomfort. Because of the pains, failing strength and loss of appetite she sought medical care.

On examination, this gray-haired woman appeared to be pale and tired. The breathing was shallow but not labored. Over the shoulders and upper thorax anteriorly several purpuric spots were visible. No bone tenderness was elicited. The pupils, fundi, and scleræ of the eyes were normal. The teeth were carious. The tongue was coated and dry. There was no palpable lymph node enlargement. Percussion resonance was somewhat impaired over the right lower thorax. Spotty areas with bronchial breath sounds and diffusely scattered moist râles were heard in both lungs. Except for a soft systolic murmur at the mitral valve area, the heart sounds were not abnormal. The blood pressure was 160 systolic, 80 diastolic. Examination of the abdomen, pelvis and rectum revealed no abnormality. Reflexes were normal.

The initial blood counts were: red blood cells, 3,130,000 per cmm.; white blood cells, 21,800; hemoglobin (Sahli), 63%. On discovering 27% plasma cells in the blood smear, a diagnosis of plasmacytoma was suggested and roentgenograms were taken. They were reported as follows:

Thorax. Cloudy density lower half right lung field.

Lumbodorsal Spine. Osteoporosis with wedge-shaped deformity of the tenth and twelfth dorsal and of the first lumbar vertebræ.

Skull. Many small punctate holes in the left lateral aspect of skull.

TABLE 1.—BLOOD FINDINGS IN CASE OF PLASMA CELL LEUKEMIA.

Date.	R. B. C. per cmm.	Hgb., %.	W. B. C. per cmm.	Differential leukocyte count, %.							
				Neutrophils.	Lymphocytes.	Atypical plasma cells.	Plasma cells.	Monocytes.	Eosinophils.	Basophils.	Myelocytes.
12/28/34 . .	3,130,000	63	21,800	47.5	22.0	3.0	24	2.5	1.0	0.0	0.0
1/ 2/35 . .	2,725,000	56	17,000	50.0	24.0	2.0	18	3.0	2.5	0.0	0.5
1/ 4/35 . .	2,830,000	57	14,150	36.5	22.5	6.5	24	3.5	3.5	0.0	3.5
1/ 9/35 . .	1,960,000	50	21,000	52.0	19.5	8.0	12	4.0	1.0	0.5	3.0
1/11/35 . .	....	..	50,150	34.0	19.5	10.0	33	2.0	0.0	0.0	1.5

Laboratory Findings. Of chief interest were the blood counts listed in Table 1. The hematocrit indices of the red cells were essentially normal. The platelets were reduced in number. The urine contained a large trace of albumin and frequently showed Bence-Jones' protein. The urine sediment consisted of a few red blood cells, white blood cells and granular casts.

The calcium and phosphorus contents of the blood were normal. The non-protein nitrogen of the blood varied from 60 to 76 mg. on three determinations. The total proteins of blood serum varied from 11.3 to 11.9 gm. per 100 cc.; the albumin fraction from 2.87 to 3.2 gm.; the globulin fraction from 7.75 to 8.8 gm.; while the fibrin content remained normal. The blood Kahn reaction was negative.

Course. During her stay in the hospital the patient became progressively weaker. An initial temperature of 102° F. subsided to normal on the second day, where it remained for 2 weeks. The pulse varied from 80 to

90 beats per minute. On the 7th day many new purpuric spots appeared over the thorax, back and forearms. On the 12th day there was blood oozing from the nose and gums. The signs referable to the lungs remained those of bronchopneumonia. The spleen and liver were not palpable. On the 14th day the temperature mounted suddenly to 102° F., and the patient became comatose and died. The clinical diagnoses were: plasmacytoma; plasma cell leukemia; bronchopneumonia.

Postmortem Examination. The body was that of a well developed, fairly well nourished elderly white woman. Ecchymotic areas of varying size were seen in the skin over the left hand and wrist, thighs, left groin and over both pectoral regions. The serous cavities were not remarkable except for firm fibrous adhesions at both lung apices and at the midportion of the right lung. The heart showed no gross abnormality. Over both pleuræ were seen a number of scattered elevated gray-white nodules 1 to 2 mm. in diameter, surrounded by a dark hemorrhagic zone. The cut surface of the lungs suggested the changes of bronchopneumonia.

The spleen was moderately enlarged, weighing 325 gm., and increased in consistence. The gastro-intestinal tract was normal except for a few scattered submucous petechiæ. In the tail of the pancreas was a soft, reddish-brown nodule 1.5 cm. in diameter. The liver weighed 1450 gm. and showed no gross changes. The kidneys weighed 300 gm. and were pale brownish-gray with a few hemorrhagic areas in the pyramids and cortex. The cancellous bone of sternum, ribs and vertebræ was thin and soft. There were no circumscribed tumor masses. The bone marrow in these areas was soft and reddish-brown. The tibial marrow contained yellow fat tissue.

Microscopic examination revealed no important changes in the heart or lungs. There was diffuse infiltration with plasma-like cells in the spleen and the liver, both in sinusoids and periportal areas. This also occurred in the kidneys, particularly in the interstitial tissue as well as in the pelvis and peripelvic fat, the abdominal lymph nodes, and in the bone marrow of the sternum, ribs, vertebræ and femurs. In the nodule in the tail of the pancreas was found a collection of plasma cells which were seen to invade the adjacent normal tissue.

The pathologic diagnoses were: (1) Findings consistent with multiple myeloma involving sternum, ribs, vertebræ and femur; (2) plasma cell leukemia; (3) plasmacytoma of the pancreas; (4) pyelonephritis; (5) bronchopneumonia.

Discussion. One essential criterion for the diagnosis of plasma cell leukemia is the constant finding of plasma cells in the blood. These are oval or round cells whose characteristic nucleus is identified by its eccentricity, a nucleolus, dense wedge-shaped chromatin masses along the nuclear membrane and a perinuclear pale area. The cytoplasm is basophilic and it may be finely granular or, if degenerated, vacuolar and foamy. In plasma cell leukemia not all cells correspond to this mature type. There also may be cells with centrally located nuclei and some forms barely distinguishable from lymphocytes.

Plasma cells appear in the blood stream in rubeola and rubella, and a few such cells are noted sporadically in other conditions as "myeloma" without leukemia, myeloid leukemia, metastatic carcinoma, and Hodgkin's disease. However, the persistent presence of a considerable number of such cells in the blood of an adult

person with the clinical picture of chronic disease is practically pathognomonic of the presence of plasmacytoma with plasma cell leukemia. In the case presented in this report provisional diagnosis was made from study of the blood smears, later to be confirmed by roentgenograms, Bence-Jones proteinuria, and high serum protein.

Exception may be taken to the term "leukemia" for this disease since the number of plasma cells in the blood is not very large and since the total white blood cell count, with few exceptions, is no higher than that occurring with moderate leukocytosis. However, the same may be true of myeloid leukemia. The term "leukemia" in these cases is justified since the condition is essentially a disease of the blood associated with changes in the spleen, liver, bone marrow and lymph nodes and characterized by a diffuse infiltration of the cell type throughout the body. Moreover, the clinical course of these cases resembles the course of other types of leukemia.

In Tables 2 and 3 are grouped the significant data of the reported cases of plasma cell leukemia. All of these exhibited diffuse infiltration of the type cell but few had impressively elevated white blood cell counts. Case 1 of Ghon and Roman[7] was included to illustrate what might be called "aleukemic plasma cell lymphadenosis." Other cases of this type have been recorded.[13, 14, 15] In several cases[6–9] the white blood cell rise and the appearance of plasma cells occurred only a few days or hours before death, as if it were an agonal expulsion of such cells. These episodes may be considered to represent a leukemic phase of leukemia which, through its early course, had been aleukemic. In 4 cases there were associated multiple myelomata;[3, 5, 6, 9] in our case an extraosseous plasmacytoma; in 6 other cases[2, 4, 7, 8, 10, 11] no associated tumors were found at autopsy.

Piney[10] and Osgood[4] emphasized the peculiarity of their cases as being instances solely of plasma cell leukemia because of the lack of associated tumor and of Bence-Jones proteinuria. However, this seems to us a needless academic nicety. The diffuse infiltration throughout the body with plasma cells occurring in the other reported cases warranted the diagnosis of leukemia whether there was an associated tumor or not. Moreover, in this disease, unless meticulously complete Roentgen ray study and search at autopsy for plasmacytoma are made, one may not confidently exclude the presence of "tumors." In neither Piney's nor Osgood's reports were such examinations available. Since Bence-Jones' proteinuria occurs in about 60% of the cases of plasmacytoma and since it occurs in other affections of bone marrow such as myeloid leukemia and metastatic carcinoma, its presence is merely confirmatory and not diagnostic of plasmacytoma (multiple myeloma). Certainly its absence is no criterion for the diagnosis of plasma cell leukemia as those authors contended. In our case Bence-Jones' proteinuria was present on some days and absent on others. It is not generally

TABLE 2.—CLINICAL FINDINGS IN REPORTED CASES OF PLASMA CELL LEUKEMIA.

Case.	Age.	Sex.	Duration of illness.	Complications.	R. B. C. per cmm.	Hgb., %	Platelets.	W. B. C. per cmm.	Plasma cells, %.	Bence-Jones proteinuria.	Roentgen ray signs of bone changes.
Aschoff, 1906	56	M	6 months	Nephritis; cystitis	....	....	....	....	Present in autopsy blood	....	....
Gluzinski, 1906	47	M	10 months	Bronchitis	2,700,000 to 680,000	50 to 15	Decreased	7600 to 39,000	Persistent 6 months: peak at 77	Positive	....
Ghon and Roman, 1913	72	F	3 weeks	Tbc. pleurisy; ?syphilis	3,750,000	61	....	13,000	2 Türck forms	....	....
	55	M	3 years	Pericarditis; pleuritis	2,500,000	..	Decreased	5600 to 6200	15	....	....
Hertz and Mamrot, 1913	32	M	5 months	Ascites	2,900,000	37	....	2900 to 19,400	5 (1 count before death)	Negative	....
Beck and McCleary, 1919	55	M	5 years	Pneumonia; nephritis	2,200,000	..	....	8800	6.6 (1 count before death)	Positive	....
Piney, 1924	48	M	6 weeks	....	2,660,000	42	....	8900 to 20,000	14 to 41	Negative	....
Muller and McNaughton, 1931	38	F	8 months	Bronchopneumonia; cystitis	4,200,000 to 2,200,000	75 to 41	Decreased	11,600 to 27,000	39 to 53	...	Positive
	46	F	9 months	Fractured spine	4,700,000	80	Decreased	50,000 to 60,000	65 (1 count)	Positive	Positive
Piney and Riach, 1931	56	M	8 months	Nephritis	3,360,000	47	....	23,000 to 42,000	16 to 33	....	....
Osgood and Hunter, 1934	49	M	6 months	....	1,400,000	30	Decreased	16,600 to 24,000	45 to 54	Negative	Positive
Cabot case Report 1935	61	F	1 year	Pulmonary infarct; nephritis	2,140,000	55	Increased	18,000	5 to 13	Positive	Positive

In the last 2 cases in which serum proteins were studied, the serum proteins were elevated.

TABLE 3.—AUTOPSY FINDINGS IN REPORTED CASES OF PLASMA CELL LEUKEMIA.

Case reports.	Liver.	Spleen.	Bone marrow.	Lymph nodes.	Miscellaneous data.
Aschoff, 1906	Not remarkable	Normal size infiltrated	Diffuse infiltration; no tumor masses	Not enlarged	Nephritis.
Gluzinski, 1906	Infiltrated	Enlarged, infiltrated	Diffuse infiltration and tumor masses	Enlarged, infiltrated	Kidneys infiltrated.
Ghon and Roman, 1913, Case I	Enlarged, infiltrated	Enlarged, infiltrated	Gray, red infiltrated; no tumor masses	Enlarged, infiltrated	Tonsils infiltrated.
Case II	Enlarged, infiltrated	Enlarged, infiltrated	Gray, red infiltrated; no tumor masses	Enlarged, infiltrated	
Hertz and Mamrot, 1913	Enlarged, infiltrated	Enlarged, infiltrated	Not examined	Enlarged, infiltrated	
Beck and McCleary, 1919	Plasma cells in sinusoids	Not mentioned	Tumor masses in ribs, sternum and clavicles; no diffuse infiltration	Cervical nodes enlarged	Chronic diffuse nephritis.
Piney, 1924	Enlarged, infiltrated	Slightly enlarged	White, firm; diffuse infiltration; no tumor masses	Cervical node enlarged and infiltrated	Kidneys infiltrated.
Muller and McNaughton, 1931	Slightly enlarged, infiltrated	Enlarged, infiltrated	Diffuse infiltration and tumor masses	Slightly enlarged and infiltrated	Kidneys infiltrated.
Piney and Riach, 1931	Enlarged, infiltrated	Enlarged	Diffuse infiltration; no tumor masses	Infiltrated	Kidneys, skin, prostate and parotids infiltrated.
Osgood and Hunter, 1934	Enlarged, infiltrated	Enlarged, infiltrated	Rib diffusely infiltrated; no palpable tumor mass; incomplete autopsy	Peri-portal nodes enlarged; infiltrated	
Cabot case, 1935	?Size; uninvolved	?Size; infiltrated	Diffuse infiltration and tumor masses	Uninvolved	

appreciated that one or two examinations are insufficient, and that marked fluctuations in this test may occur during 24 hours.

The finding of both plasmacytoma and leukemia in the case now reported appears to confirm the theory advanced by Lubarsch[12] and Pappenheim,[16] emphasized by Ghon and Roman and others, and reiterated by Jackson, Parker and Bethea[17] that there are comparable gradations in plasma cell tumors analogous to lymphomata. Thus there may be single and benign or multiple and relatively malignant plasma cell tumors. There may be a diffuse cellular infiltration throughout the body, and this in turn may proceed with or without changes in the peripheral blood stream. Moreover, as in certain of the reported instances, several forms may coëxist.

We wish to reassert the desirability of regarding this plasma cell tumor (plasmacytoma) as a pathologic entity whose different forms are not distinct diseases, but are simply gradations in extent and activity of the same disease process.

Summary. A case of plasmacytoma with plasma cell leukemia is reported together with a brief analysis of 11 such cases recorded in the literature.

It is believed that the plasma cell tumor should be regarded as a pathologic entity whose different forms are simply gradations in extent and activity of the same disease process.

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THE EFFECT OF ROENTGEN RAY IRRADIATION ON PLATELET PRODUCTION IN PATIENTS WITH ESSENTIAL THROMBOCYTOPENIC PURPURA HÆMORRHAGICA.*†

By Stacy R. Mettier, M.D.,
ASSISTANT PROFESSOR OF MEDICINE,
AND
Robert S. Stone, M.D.,
ASSOCIATE PROFESSOR OF ROENTGENOLOGY, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL, SAN FRANCISCO, CALIF.

With the Technical Assistance of
Katherine Purviance, A.B.

(From the Divisions of Medicine and Roentgenology, University of California Medical School, San Francisco, Calif.)

Bleeding in idiopathic purpura hæmorrhagica has long been known to be accompanied by thrombocytopenia.[1, 2] When the blood platelets become reduced to a sufficiently low level, capillary hemorrhages appear in the skin following slight trauma or venous stasis, the bleeding time is increased, and there is a failure of the clot to retract. Since it is generally accepted that the blood platelets play an important rôle in thrombus formation and clotting, this deficiency, in addition to increased fragility of the capillaries, is used as a possible explanation for the development of purpura. There is little to be found in the medical literature, however, on the favorable influence of therapeutic procedures on platelet production in this disease. Kaznelson[3] demonstrated in 1916 a thrombocytosis following splenectomy. Since then, drugs, some possibly of minor importance, which have been employed with supposedly beneficial results, are foreign protein-shock therapy, liver extract, both by mouth and parenterally, iron, ergot, snake venom,[4, 5] ascorbic acid[6] and many others. Remarkably few studies, however, have been reported on the effect of Roentgen ray radiation on the number of circulating blood platelets in idiopathic thrombocytopenic purpura. Bucky and Guggenheimer[7] claim to have demonstrated a rise in blood platelets following stimulative doses of Roentgen ray over the spleen. Other reports[8, 9] do not contain actual platelet counts, but present evidence showing cessation of hemorrhage in patients for varying periods of time after radiation, and thus lend support to the value of this form of therapy. Marzullo,[10] on the contrary, failed to find significant clinical improvement in his patients after Roentgen ray therapy and stated that in 1, notwith-

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standing cessation of hemorrhage, the platelets did not rise above 100,000 per c.mm. In addition, the recent reports of various authors[11,12,13] on the treatment of purpura hæmorrhagic omit any discussion on the effect of Roentgen ray radiation. In view of the fact that there has been some controversy over the efficacy of Roentgen ray treatment on patients with idiopathic purpura hæmorrhagica, and since the platelet deficiency is of considerable importance in the causation of hemorrhage, it seemed to us desirable to make a careful estimation of the platelets in the circulating blood of patients with this disease before and after the administration of a known Roentgen ray dosage.

Method of Study.—Seven patients, 4 females and 3 males, varying in age from 4 to 67 years, comprised the series for this study. The criteria used in the diagnosis of purpura hæmorrhagica were the spontaneous appearance of petechial hemorrhages and ecchymoses in the skin; an increased capillary fragility; prolonged bleeding after puncture of the lobe of the ear; a failure of the clot to retract; and a marked reduction in the number of platelets. The patients could be divided into 3 groups, depending upon duration and severity of symptoms. Four of the patients had acute recurring thrombocytopenia with purpuric symptoms, 2 had chronic thrombocytopenia with recurring purpura and 1 patient had an acute fulminating type of purpura.

Platelet counts were done daily while the patients were in the hospital for treatment and at intervals of approximately 1 week to 1 or more months after discharge. The platelets were counted after the manner described by Rees and Ecker.[14] The fluid used for dilution was prepared according to the directions recommended by these authors and was filtered each time before use. A pipette calibrated for the enumeration of erythrocytes and certified for accuracy by the U. S. Bureau of Standards was used in the determination of the number of platelets per cubic millimeter of blood. After dilution the pipette was shaken for 5 minutes, the counting chamber loaded, but actual counting was not done until 10 minutes had elapsed to permit sedimentation of the platelets. The erythrocytes and leukocytes were counted in the usual manner. The hemoglobin determinations were made on the Sahli hemometer calibrated to read 14 gm. to 100 cc. of blood.

The determination of capillary resistance was estimated by the use of a sphygmomanometer with the cuff inflated to a pressure just below the systolic and sustained for 5 minutes. A definitely positive result was recorded if innumerable petechial hemorrhages appeared in the skin of the forearm.

During the period of Roentgen ray administration all other forms of therapy which might influence platelet production were omitted. In treating these patients the following factors were used: 200 kilovolts, constant potential; 15 milliamperes; target skin dis-

tance of 50 cm., composite filter consisting of 0.2 mm. of tin, plus 0.25 mm. of copper, plus 2 mm. of aluminum.

Using the above factors, the apparatus delivers 28.2 roentgens per minute, measured without backscatter. The size of the field used on the patient's skin varied with the size of the patient and the size of the spleen. The smallest was 10 by 10 and the largest, 10 by 20 cm. The rays were directed toward the spleen from the front, from the back and from the side. One field a day was used. The daily dose varied between 200 r. and 300 r., with a total of from 1200 to 3300 r. in 6 to 15 days.

Effect of Roentgen Ray on Platelet Production in Acute Recurring Thrombocytopenia. The 4 patients in this group showed a definite increase in their circulating blood platelets following Roentgen ray radiation over the spleen. It is to be noted in Figs. 1, 2 and 3 that the platelet response was prompt, and began within 24 to 48 hours after treatment was started. In 2 patients receiving a total of 1200 r. units (Figs. 1 and 3), the platelets rose from a level of less than 40,000 before treatment to that of 300,000 or more per c.mm. during the period in which the 10 days' treatment was continued. In another patient (Fig. 2), less intense treatment, namely, a total of 800 r. units, was given and a lapse of approximately twice this period of time occurred before the platelets attained a high peak. In Protocol 4 are the data on a female patient, aged 9 years, whose recurring purpura had been previously controlled by transfusions. After Roentgen ray therapy to the spleen, this young patient had a rise in blood platelets from a level of about 100,000 to 500,000 per c.mm. followed by a cessation of bleeding.

Coincident with the platelet response, it is to be noted in the protocols that there was a gradual lessening of the hemorrhagic tendency and a subsequent return to normal of the clotting mechanism. In addition, in 3 patients who had had increased fragility of the capillaries prior to treatment, the tourniquet test showed a negative response 10 days after treatment was first started.

It is of interest to note in Fig. 1 that a decrease in platelets occurred after treatment was stopped and progressed to a marked thrombocytopenia. A recurrence of purpuric symptoms occurred in this patient (Case 1) 7 months after the first attack of purpura. At this time a second course of Roentgen ray was given to the spleen and consisted of a total dosage of 1800 r. units administered over a period of 12 days. Again there was a prompt rise in platelets from a level of about 40,000 to over 300,000 per c.mm. within ten days.

A recurrence of thrombocytopenia and bleeding also occurred in the patient whose data are recorded in Fig. 3. A total second dosage of 3500 r. units was given to the spleen over a period of 12 days and was accompanied by a thrombocytosis and a disappearance of spontaneous bleeding. This patient had been taking

Sedormid just prior to both the first and second attacks, which may be of some etiologic significance.[15] A photograph of a stained film of the blood from this patient showing the absence of platelets is reproduced in Fig. 4 and another showing their reappearance after Roentgen ray radiation is reproduced in Fig. 5.

The subsequent course of the platelets in 2 of the patients is also shown in Figs. 1 and 2. In the first patient the platelets have remained above 300,000 per c.mm. for 3 months, and in the second patient, above this level for 7 months.

It is to be emphasized that a second favorable response in 2 patients following Roentgen ray radiation over the spleen lends considerable support to the idea that this form of therapy in adequate dosage does increase the number of circulating platelets.

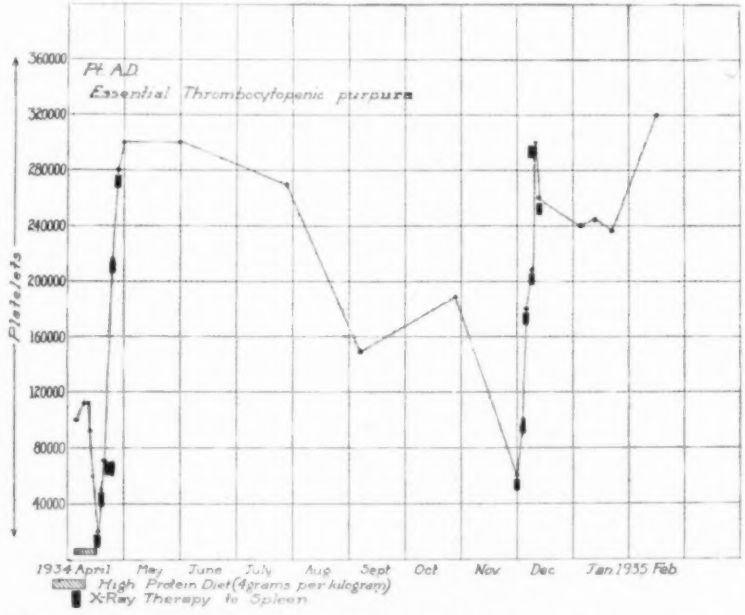

FIG. 1.—Effect of Roentgen ray radiation over the spleen on a patient (Case 1) with essential thrombocytopenic purpura hemorrhagica. Note the recurrence of thrombocytopenia and a second response to treatment.

Protocol. CASE 1.—A. D., a white American woman, aged 24, entered the University of California Hospital, April 3, 1934, stating that 2 months prior to hospital entry she had noticed the spontaneous occurrence of small hemorrhagic spots in the skin of the left breast. Since then, punctate purpuric spots had appeared at various places on her body. Associated with this was a marked tendency to bruise easily. Recently there had been slow oozing of blood from the gums and 4 brief periods of epistaxis. During this time her menses had been more profuse than usual. There was no history of the use of drugs, infections, or the association with chemi-

cals which might account for this hemorrhagic tendency. She had partaken of a well-balanced diet, including an abundance of vitamin C in fresh fruits and vegetables.

Physical Examination. On admission she appeared fairly well nourished and developed. There were small purpuric spots distributed over the body and there was a slight oozing of blood from the gums. There were no palpable lymph nodes in the cervical, axillary or inguinal regions, but there was slight splenic enlargement.

Laboratory Data. Examination of the blood showed: Erythrocytes, 4,160,000 per c.mm.; white blood cells, 5500 per c.mm.; and a hemoglobin concentration of 97% (13.6 gm., Sahli). The platelets were 112,000 per c.mm.; bleeding time, 25 minutes; clotting time within normal limits, but there was failure of the clot to retract. The tourniquet test was strongly positive for the appearance of petechial hemorrhages after 5 minutes' application.

Course of Illness. Within 9 days of hospital entry the platelets had dropped to 30,000 per c.mm., and by this time the patient had developed a slight hypochromic anemia. A high-protein diet was prescribed, calculated to yield 4 gm. of protein per kilogram of body weight. Bleeding became more profuse from the gums, epistaxis appeared, and large ecchymoses developed in the skin. Nine days after entry Roentgen ray treatment was started, and 6 exposures were given over a period of 12 days, at the end of which time bleeding had entirely subsided. The patient was discharged from the hospital, April 2, 1934, at which time the platelet count was 300,000 per c.mm.

On November 30, 1934, there was a slight recurrence of the hemorrhagic tendency, and at this time the platelets were 60,000 per c.mm. Over a period of 12 days 1800 r. units were administered and again the platelets rose to 300,000 per c.mm. The subsequent course of the platelets is recorded in Fig. 1.

Case 2.—D. R., a white unmarried female, aged 23, was admitted to the University of California Hospital, September 19, 1934, complaining of epistaxis and bleeding gums of 4 months' duration. Three years prior to entry she had several episodes of epistaxis, prolonged bleeding when cut, menorrhagia, and bruised easily with slight trauma. After a few months this tendency to bleed lessened until the present illness. In the past she had had frequent coryza, occasional infection in the throat, and for many years had recurring acne scattered over her body. She had not used drugs nor had she knowingly been exposed to chemicals which might account for her condition. She had subsisted on an adequate diet.

Physical Examination. The patient was well developed and nourished. There was no apparent infection of the throat, but there were some small acneform pustules in the skin of the face and back. No enlarged superficial lymph nodes could be felt. The tip of the spleen was felt 2 cm. below the left costal margin. There were some bloody incrustations in the right nostril and some recent and fading ecchymoses in the skin of the lower extremities. The application of the sphygmomanometer with the cuff inflated to a pressure just below the systolic showed the presence of large numbers of petechiæ in the forearm at the end of 5 minutes.

Laboratory Data. Examination of the blood showed: Erythrocytes, 4,310,000 per c.mm.; hemoglobin, 66 % (9.2 gm., Sahli); leukocytes, 9000 per c.mm. The bleeding time was slightly prolonged and retraction of the clot did not occur until the end of 12 hours.

Course of Illness. Between September 24 and October 3 the patient received 4 Roentgen ray treatments over the spleen, with a total dosage of 800 r. units. Twenty days after treatment was started the platelets were 210,000 per c.mm., the bleeding time 3 minutes and the clot retraction

normal. Six months after treatment the platelets were 420,000 per c.mm. The course of the platelets in this patient are recorded in Fig. 2.

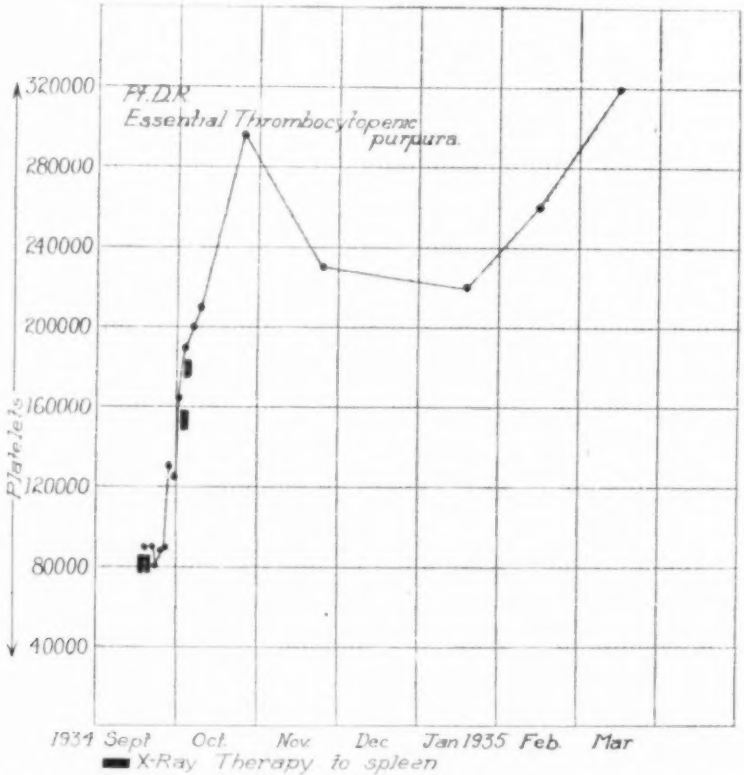

FIG. 2.—A slightly delayed reaction in a patient (Case 2) receiving less intense radiation.

CASE 3.*—M. C., an Italian female, aged 67, had been under the care of her physician for essential hypertension, arteriosclerosis and diabetes mellitus. Medication had consisted of insulin, digitalis folia and Sedormid tablets for pain. Her first entry into the hospital was November 18, 1934, at which time she complained of hemorrhagic spots on her legs and bleeding from the gums of 2 days' duration. The day prior to entry she had noticed blood in the urine. She had never noticed a hemorrhagic tendency until the present illness.

Physical Examination. The patient was moderately obese. There was no apparent ulceration of the pharyngeal structures. No large lymph nodes could be felt. The spleen was not palpable on deep inspiration. There were scattered purpuric spots and ecchymoses over the entire body but particularly on the arms and legs. There were petechial hemorrhages on the conjunctivæ and a small amount of blood was oozing from the nasal passages and from the gums. The tourniquet test was strongly positive for capillary hemorrhages.

* We express our thanks to Dr. John Sampson for permission to study this patient.

Laboratory Data. Examination of the blood showed: Erythrocytes, 4,470,000 per c.mm.; leukocytes, 10,800 per c.mm.; platelets, 40,000. The clotting time was 25 minutes and the clot failed to retract.

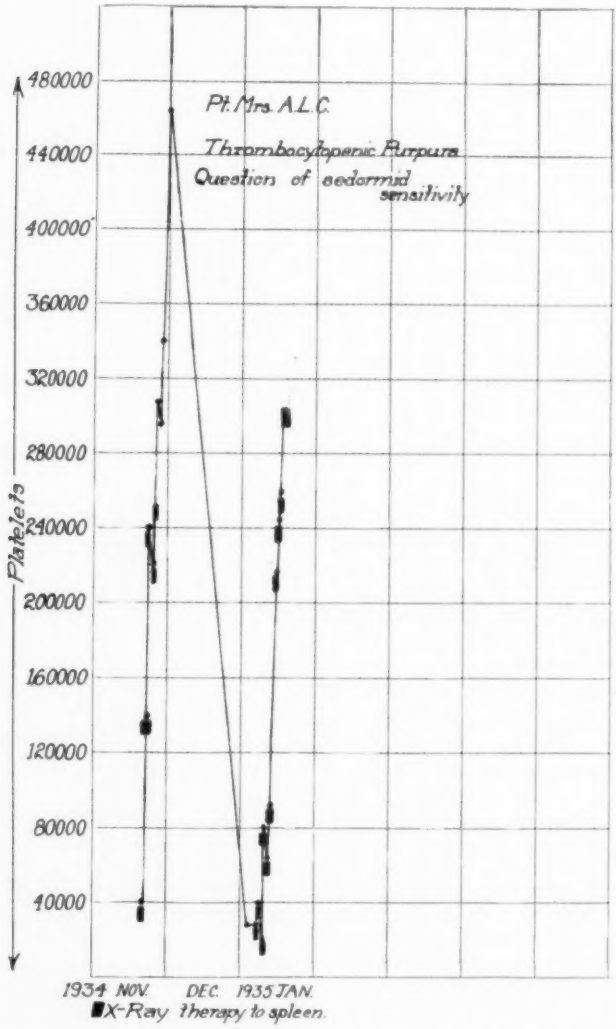

FIG. 3.—Effect of Roentgen ray radiation of the spleen on a patient (Case 3) with recurring thrombocytopenia believed due to Sedormid sensitivity.

Course of Illness. Roentgen ray therapy over the spleen was started on the day of entry, and after 6 exposures, 1 given on each successive day, the platelets had risen to 300,000. Application of the sphygmomanometer failed to show the presence of petechial hemorrhages. The bleeding tendency disappeared and the patient was discharged from the hospital,

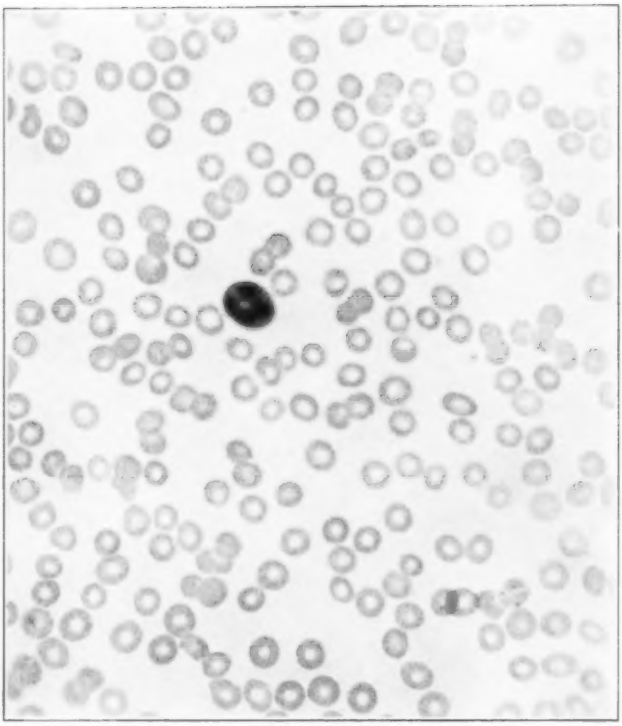

FIG. 4.—A typical field from a blood smear of Case 3 before Roentgen ray treatment. Note the absence of platelets.

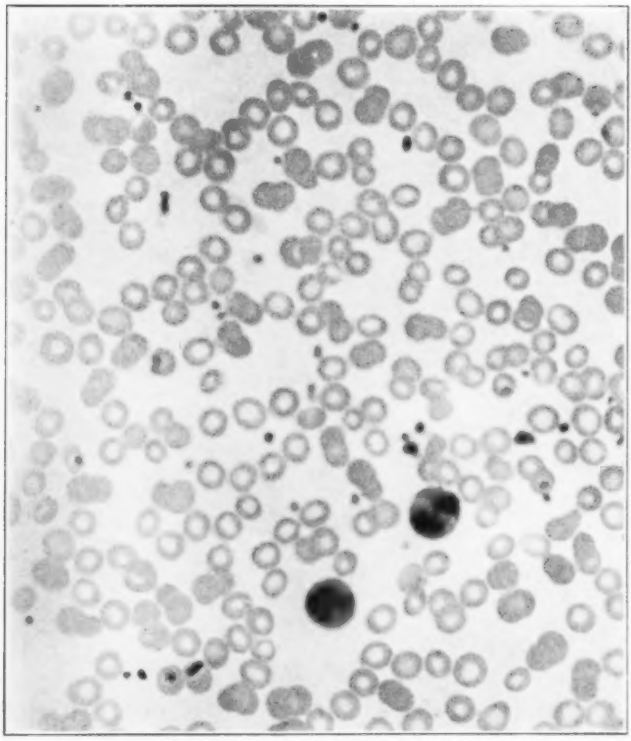

FIG. 5.—A typical field of a blood smear from Case 3 after Roentgen ray radiation. Note the presence of large numbers of platelets.

November 30, at which time the platelets were 468,000 per c.mm. Bleeding time was 1½ minutes and there was normal retraction of the clot. The patient was seen on January 4, 1935, when again she showed marked bleeding from mucous membranes and into the skin. The platelets were 30,000 per c.mm. The bleeding time was longer than 25 minutes and there was failure of the clot to retract. It was learned that she had started taking Sedormid tablets just prior to the onset of this second episode of bleeding. Roentgen ray therapy was started on January 7, and the patient was given treatment over the spleen daily for a total of 11 exposures, or 3300 r. units. On January 8, the platelets were 300,000; the bleeding time, 3½ minutes, with a normal retraction of the clot. Data showing Roentgen ray therapy and the course of the platelets in this patient are shown in Fig. 3.

CASE 4.—V. D. S., a schoolgirl, aged 9, entered the San Francisco Hospital, May 5, 1935, because of bleeding from the mouth and hemorrhages in the skin of the abdomen and legs. She had had 2 previous hospital admissions at about 10 months' intervals. On these occasions her symptoms were similar and her blood platelets were about 85,000 per c.mm. A diagnosis of thrombocytopenic purpura was made. Treatment consisted of the intravenous administration of whole blood followed by a subsidence of her symptoms. The child had been fairly well until the present entry, except that she had noticed slight bleeding from the gums on occasions. On the day of entry she developed profuse bleeding from the gums and several hemorrhages appeared over her body. There was no history of medication or exposure to chemicals which might account for the bleeding. She had eaten on the average of 1 orange a week.

Physical Examination. The patient was well nourished and developed, active, coöperative, intelligent and resting quietly in bed. There were no demonstrable enlargements of the lymph glands and the spleen was not palpable. There was no evidence of infection. Blood was oozing slowly and continuously from the gums, and there were many petechial and ecchymotic hemorrhages scattered over the body.

Laboratory Data. The red blood cells were 4,200,000 per c.mm., and the leukocytes 8600 per c.mm., with a normal differential count. The hemoglobin was 80% (Sahli). A specimen of venous blood clotted in 7 minutes, but there was a failure of the clot to retract. Following a puncture of the ear, bleeding continued for 32 minutes. The platelets were about 100,000 per c.mm.

Course of Illness. The patient received Roentgen ray treatment over the spleen consisting of 200 r. units daily, alternating anteriorly and posteriorly for 8 days, making a total of 1600 r. units. Seven days after treatment was started, the laboratory data showed the bleeding time to be reduced to 8 minutes and the platelets increased to 500,000 per c.mm. One week later the laboratory data were essentially the same.

Effect of Roentgen Ray Therapy on Patients With Chronic Thrombocytopenia With Recurring Purpura. The course of illness in 2 of our patients was characterized by recurring purpura and various forms of treatment for the control of bleeding had been tried off and on over a period of 1 or more years. Such therapeutic agents were given as daily injections of liver extract (343 NNR), large doses of iron by mouth (iron and ammonium citrate, U. S. P., 6 gm. daily), calcium by mouth and a diet high in calcium, spleen marrow, lextron, pentnucleotide and multiple transfusions. The best results, so far as cessation of bleeding was concerned, were obtained from

repeated transfusions, but with any of the methods there was little or no actual increase in the total number of platelets.

In Fig. 6 are shown a summary of the treatment and the graphic presentation of the platelets of a patient (Case 5) who was observed over a period of 22 months. The platelets during this time varied between 40,000 and 80,000 per c.mm., going as high as 120,000 on one occasion after 3 transfusions of whole blood. It is to be noted in the figure that following Roentgen ray treatment over the spleen this patient's platelets rose to a peak of 270,000 per c.mm. Coincident with this, the loss of blood from the gums stopped and the petechial hemorrhages which had accompanied the thrombocytopenia gradually faded. In addition, a specimen of blood coagulated within normal time and soon after developed a firm retractile clot. It is of interest to note, however, that the platelets did not remain at a high level, but 6 weeks after treatment was first started had returned to a low figure of 120,000 per c.mm.

The diagnosis of the disease from which this patient (Case 5) and the following one (Case 6) suffered is not clear-cut, but the data suggest that of chronic thrombocytopenic purpura with anemia, rather than chronic aplastic anemia, aleukemic leukemia, or depressed marrow function as a result of infection or neoplasm.

In Fig. 7 is recorded the course of the platelets in a patient (Case 6), aged 4 years, who had had recurring attacks of thrombocytopenia and purpura while under observation for a year. During this time small transfusions of whole blood given at frequent intervals on 3 different occasions and finally splenectomy caused a rise in platelets from about 40,000 to as high as 80,000 per c.mm. It was at first thought that the patient had an accessory spleen which might account for the recurrence of symptoms after splenectomy, and, with this in mind, it was decided to give him Roentgen ray radiation over the abdomen. This was not done, however, and in its stead treatment was directed over the long bones. In Fig. 7 it is to be noted that a sharp rise in platelets from a low level of 60,000 per c.mm. occurred soon after treatment was started and within 9 days reached a peak of 270,000. As in the previous case, however, the platelets began to decrease after treatment was stopped.

Protocol. Case 5.—J. S., a married male, aged 60, was first seen, February 3, 1935, and has been under observation since that time. He has had recurring attacks of epistaxis, bleeding from the gums, petechial hemorrhages in the skin, and had noticed that he bruised easily with slight trauma. He has also had symptoms of dyspnea and palpitation following exertion.

Physical Examination. A moderately obese, well-developed, pale man of stated age. There were no enlarged lymph glands and the spleen was not enlarged. There was no evidence of heart disease. During the past 2 years, the number of red blood cells varied between 750,000 and 3,000,000 per c.mm., and the percentage of hemoglobin varied between 10 and 75%

(Sahli). The number of leukocytes varied between 2000 and 6000 per c.mm. Repeated differential counts revealed normal percentages, with the exception of the presence of from 1 to 5% myelocytes and from 10 to 20% of non-filament cells. Rarely was a cell similar to a myeloblast observed. The percentage of the reticulocytes was always slightly increased, the highest figure being 6 and the lowest 2. The blood platelets were reduced and varied in numbers from 40,000 to 100,000 per c.mm. The bleeding time was over 25 minutes and many petechial hemorrhages appeared after the tourniquet test. Coagulation time was 4½ minutes, but the clot was friable and did not retract.

Course of Illness. The Roentgen ray therapy, consisting of a total of 1200 r. units, and the course of the platelets in this patient are recorded in Fig. 6.

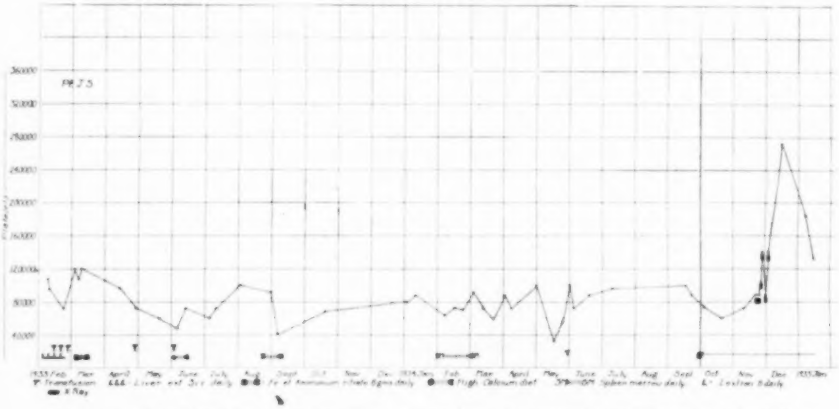

FIG. 6.—Showing the negative effect of various therapeutic measures on platelet production in a patient (Case 5) with chronic thrombocytopenia but a definite increase after Roentgen ray radiation.

CASE 6.*—R. S., a boy, aged 6, was first seen, January 9, 1934, complaining of slight epistaxis and bruising of the skin of 2 years' duration.

Physical Examination. The patient was undernourished and there were fading ecchymoses in the skin. The spleen was slightly enlarged.

Laboratory Data. Examination of the blood at frequent intervals during the past year showed a variation in the number of red blood cells between a level of 1,000,000 to 3,000,000. The white blood cells fluctuated between 1200 and 8000. Repeated differential counts revealed normal percentages of the various white blood cells. Prior to Roentgen ray therapy, the platelets were markedly reduced and varied in numbers between 30,000 and 100,000 per c.mm. The capillary clotting time was 10 minutes. The clot did not retract.

Course of Illness. Various therapeutic agents and multiple transfusions were tried on this patient without definite effect on the platelet count. Cessation of the hemorrhagic tendency did occur for short periods of time after transfusion. Finally, the patient was given transfusions in the amount of 200 cc. of whole blood daily for 6 days, followed by the removal of the spleen. The platelets at this time were 80,000 per c.mm., and

* The authors wish to thank Dr. F. S. Smyth, of the Division of Pediatrics for permission to study this patient.

within 2 months had dropped to less than 60,000 per c.mm. It was considered advisable at this time to give the patient Roentgen ray treatment over the long bones. Data relative to treatment and the platelets in this patient are reported in Fig. 7.

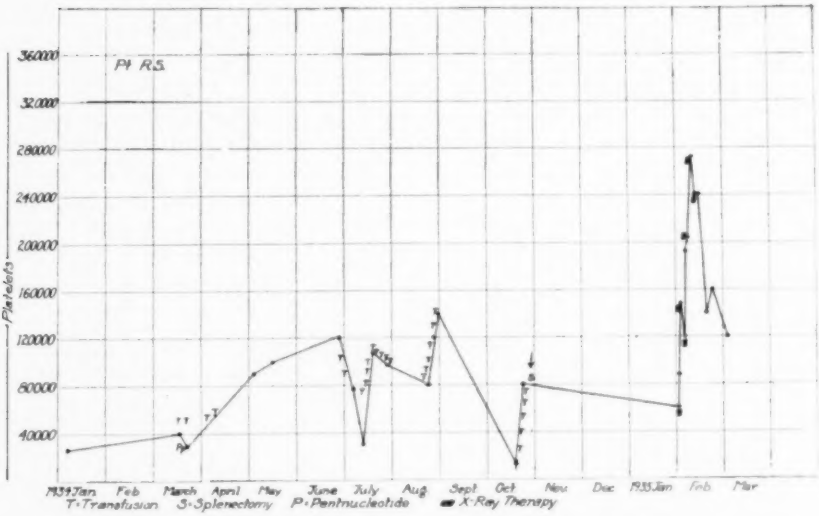

FIG. 7.—Showing a moderate increase in platelets in a patient (Case 6) following multiple transfusions; no effect after splenectomy but a marked rise after Roentgen ray of the long bones.

TABLE 1.—SHOWING LABORATORY DATA AND COURSE OF ILLNESS ON CASE 7.

Name: Mr. R. H. Age: 40 Sex: ♂

Diagnosis: Idiopathic Purpura Hæmmorhagica (Fulminating Type)

Date.	R.B.C.	Hgb. % Gm.	Platelets.	W.B.C.	X-Ray.	Notes.
1–5–35	4.81	94–13.1	40,000	12,800	×	Bleeding time 14½ minutes +. Coagulation time 8 minutes.
1–7–35	2.35	54–7.6	20,000	21,800	×	5 P.M. — 200 cc. transfusion.
4 P.M.	2.23	43–6.0	30,000			
1–8–35 9 A.M.	2.04	32–4.5	None seen in counting chamber	20,100	×	Splenectomy—1.30 P.M.
2.00 P.M.	1.45	35–5.0	30,000	70,400	..	Count made 5 minutes after splenic vessels clamped.
4.10 P.M.	1.38	32–4.5	78,000	....	..	Patient died 12 o'clock midnight

The Ineffectiveness of Therapy in Acute Fulminating Purpura. In Table 1 are presented the data on a middle-aged man (Case 7), who entered the hospital with an acute type of idiopathic purpura hæmorrhagica progressing to a fatal termination. It is to be

noted that at the time of entry this patient's red blood cells and hemoglobin were within normal limits, but there was a marked reduction in the number of platelets. Roentgen ray therapy was given to this patient in the same way it was given to the others. Despite this régime, however, there was a progression of the hemorrhagic tendency and the rapid development of a severe anemia. Finally, splenectomy was performed and was followed 12 hours later by the death of the patient from hemorrhage.

Protocol. Case 7.—R. H., a man, aged 40, entered the University of California Hospital, January 4, 1935, complaining of bleeding from the nose and gums and of bloody urine. The day prior to entry the patient awakened in the morning and found his mouth full of blood. He went to a physician who told him that he was bleeding from the nose and gums. During the night he noticed, for the first time, bloody urine. His occupation was that of a salesman, and he knew of no exposure to benzol, arsenic, lead or other heavy metal or Roentgen ray. The only drug consumed was aspirin, in daily amounts of 10 to 20 grains, at varying intervals during the past 3 weeks. Three weeks prior to the present illness he had had an upper respiratory infection, but there were no symptoms referable to this condition during the past week. There was no past history of bruising easily or of prolonged bleeding.

Physical Examination. The patient was well developed and nourished, quite apprehensive and showed continuous bleeding from the nose and gums, and there were large hemorrhagic blebs beneath the mucous membrane of the mouth. Scattered over the entire body were petechial hemorrhages and small ecchymoses. No enlarged glands could be felt and the spleen was not enlarged to palpation. The tourniquet test was markedly positive for petechial hemorrhages.

The laboratory data and the course of the disease for this patient are shown in Table 1. It is to be noted that in spite of Roentgen ray therapy, transfusion and splenectomy, the disease was progressive and the patient died 5 days after the onset of illness.

Discussion. From our observations presented here, it appears that by Roentgen ray radiation in adequate dosage over the spleen or long bones, an increase in blood platelets will occur in patients with essential thrombocytopenic purpura hæmorrhagica. Accompanying this there is a cessation of bleeding and a disappearance of the hemorrhagic tendency.

It is difficult to explain this phenomenon adequately. The rise in platelets begins soon after 1 or 2 treatments and, accordingly, before a sufficient number of radiations have been given to cause marked destruction of splenic tissue. Apparently, the reaction is not one of so-called "Roentgen ray splenectomy," and, therefore, the response is not similar to the thrombocytosis that follows surgical removal of the spleen.

One of the theories concerning causation of thrombocytopenia is that of phagocytosis of platelets by cells of the reticulo-endothelial system. In view of this idea, it may be suggested that Roentgen ray radiation either prevents the continuation of this process or causes a release of platelets already engulfed.

There is now considerable evidence[16, 17] at hand to support Wright's theory that the megakaryocytes of the bone marrow are chiefly concerned in the production and release of the blood platelets. We have insufficient data to prove that platelet production following radiation is a result of increased activity of the megakaryocytes. Since treatment was directed over the spleen in all of our patients with but one exception, there is very little to suggest any direct effect of this form of therapy upon the megakaryocytes. Further work is indicated wherein studies on bone marrow removed by biopsy from patients under treatment may be correlated with platelet production.

It is quite evident from our results that Roentgen ray therapy is not entirely satisfactory so far as curative results are concerned. In some of our patients a recurrence of symptoms appeared from 1 to 7 months after treatment was stopped. It is to be emphasized, however, that a rise in blood platelets did occur in 6 out of 7 of our patients.

Summary and Conclusions. Seven patients with essential thrombocytopenic purpura comprised a series for study on the effect of Roentgen ray therapy in platelet production. Prior to treatment the platelets were about 10,000 per c.mm. in 1 patient and varied between this figure and 40,000 in the others. Six patients received Roentgen ray therapy over the spleen and 1 over the long bones in doses of 200 r. units. Two patients had a recurrence of symptoms and were given 300 r. units during a second course of treatment. The patients received a total of from 1200 to 3300 r. units. Six of these patients showed an increase in platelets, beginning within 24 to 48 hours, going up to as high as 250,000 to 500,000 per c.mm. in 9 days. In 1 patient with chronic thrombocytopenia of 2 years' duration, no effect was shown following liver extract therapy, multiple transfusions, large doses of iron and ammonium citrate daily, high-calcium diet, spleen marrow or lextron, but a definite rise in platelets occurred following Roentgen ray treatment. In 1 patient a high-protein diet failed to increase the platelets, but there was a rise after Roentgen ray treatment. In another patient there was a recurrence of symptoms following splenectomy and an increase in platelets was stimulated by Roentgen-ray therapy over the long bones. In still another patient no increase of platelets was produced by Roentgen ray or splenectomy and the patient died as the result of hemorrhage.

It is concluded from these studies that Roentgen ray radiation of the spleen in doses of from 200 to 300 r. units will cause an increase in blood platelets in patients with idiopathic thrombocytopenic purpura hæmorrhagica.

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POSTOPERATIVE RESPIRATORY COMPLICATIONS: OCCURRENCE FOLLOWING 7874 ANESTHESIAS.

By E. A. Rovenstine, M.D.,

ASSISTANT PROFESSOR OF SURGERY IN CHARGE OF ANESTHESIA, NEW YORK UNIVERSITY MEDICAL SCHOOL; DIRECTOR OF ANESTHESIA, BELLEVUE HOSPITAL; FORMERLY ASSISTANT PROFESSOR OF ANESTHESIA, UNIVERSITY OF WISCONSIN HOSPITAL,

AND

Ivan B. Taylor, M.D.,

ASSISTANT DIRECTOR OF ANESTHESIA, BELLEVUE HOSPITAL, NEW YORK; FORMERLY RESIDENT ANESTHETIST, UNIVERSITY OF WISCONSIN HOSPITAL, NEW YORK CITY.

(From the Department of Anesthesia, University of Wisconsin Medical School.)

Pulmonary complications following anesthesia with certain of the agents, have been thought to greatly exceed such complications after the use of other agents. Writers have pointed out an advantage with nitrous oxid, spinal and other anesthetic drugs since they are

not irritant to the respiratory tract and do not increase secretions. Too often such reports have not been substantiated by accurate, carefully collected statistics. They may merely represent the author's impression or may consider one single factor, namely the agent. It has been a firm conviction in this clinic that other factors such as the ability of the surgeon and anesthetist, the anesthetic technique, the time required for operation, the depth of narcosis and many other circumstances should be taken into account in evaluating postoperative morbidity and mortality. It was to correlate the majority of the factors common to surgical procedures and learn their influence on postoperative pulmonary complications that the present study was undertaken.

It is readily agreed that statistics are not infallible but if they are carefully recorded and tabulated they offer a worthy substitute for vague conclusions which cannot be verified by records. The statistics in this report were compiled from the records completed during the calendar years 1933–1934. They represent the first 2 year's experience with an improved anesthetic record system at the Wisconsin General Hospital.[1]

All anesthetics included in this report were administered by members of the Department of Anesthesia. Minor operations completed with local infiltration anesthesia by the surgeon are not considered. Senior medical students who spend 1 week on the service, interns for the month of their rotating service spent in anesthesia, residents of 1 or 2 years' experience, the assistants and the chief of the service comprise this department. The surgery was performed by the same staff under similar conditions in a single hospital. The anesthetic agents included were those in common use: ether, nitrous oxid (N_2O), ethylene (C_2H_4), tribromethanol (T. B. E.), procain, together with cyclopropane (C_3H_6) an experimental drug unfamiliar to the staff before 1933. Chloroform, barbituric acid derivatives and other drugs used in less than 100 cases were not included.

The statistics were carefully collected by the anesthetic department after a definite scheme. The patient was visited before operation and the clinical record examined. The patient was seen postoperatively on the third to fifth day. If complications were present, later visits were made. Finally the case was reviewed to complete the record at time of discharge or death. Such data were transferred to a punch card and tabulated by machine.[1]

Premedication varied little. Morphin and scopolamin were given to most of the cases. A barbituric acid derivative was given to patients when procain anesthesia was anticipated. Atropin was used occasionally. Obstetrical cases, infants, and some others usually had no premedication.

Table 1 lists the complications considered in this report. The number of times each complication was noted and the percentage

incidence are listed. No effort has been made to differentiate complications as due to surgery, anesthesia or the preëxisting condition of the patient. A very liberal interpretation of complications was made. None were omitted. Respiratory complications present before operation were not listed as postoperative complications in those cases where surgery was undertaken as a treatment for the condition. For example, a patient with pulmonary tuberculosis treated by thoracoplasty was not considered as having tuberculosis as a postoperative complication. However, a patient coming to surgery with pharyngitis or cough was recorded as having pharyngitis or cough postoperatively if the condition was aggravated by surgery or in any way complicated convalescence. The item "sore throat" in Table 1 was used to designate resulting trauma in cases anesthetized by endotracheal technique. The same complication following the use of any other technique was listed as laryngitis.

TABLE 1.—RESPIRATORY COMPLICATIONS IN 7874 ANESTHESIAS.

Complications.	No.	Percentage of all cases.
Pneumonia, lobar and bronchial	49	0.60
Pneumonia, hypostatic	8	0.10
Pneumonia, tuberculosis	2	0.02
Collapse, partial	22	0.30
Collapse, massive	13	0.20
Bronchitis	22	0.30
Laryngitis	144	1.80
Cough, slight	287	3.60
Cough, severe	89	1.10
Hiccough	35	0.40
Obstruction, upper respiratory	32	0.40
Rhinitis	27	0.30
Pleurisy	11	0.10
Sore throat*	33	0.40
Miscellaneous	24	0.30
All respiratory complications	..	6.00

* Endotracheal anesthesia only.

The time of occurrence of the complications shown in Table 1 varied greatly. The postoperative period was not limited to any definite number of days. A pneumonia developing on the fourteenth day following inguinal herniorrhaphy would be included, while the same complication occurring as a terminal event months after a celiotomy in an inoperable carcinoma case would be excluded and the cause of death given as carcinoma. An effort was made to include every major and minor respiratory complication that might possibly be related to the surgical procedures regardless of when it occurred.

Figure 1 graphically represents the percentage incidence of respiratory complications for each month of the year. During the first year of the study an attempt was made to correlate respiratory complications with average temperatures and humidities. Postoperative complications could not be anticipated from existing

weather conditions. Certain factors such as a severe dust storm during July, 1934, may explain an increase of respiratory complications that month.

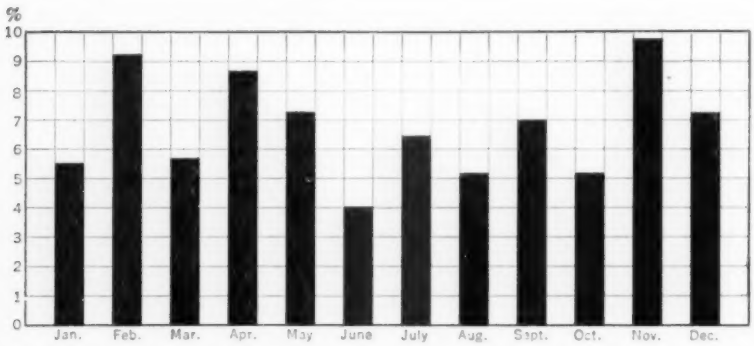

FIG. 1.—Percentage incidence of respiratory complications for each month.

It was definitely established for the year 1933 that the incidence of postoperative respiratory complications was greater during the same months that respiratory diseases had an increased prevalence among university students as shown by student health records.

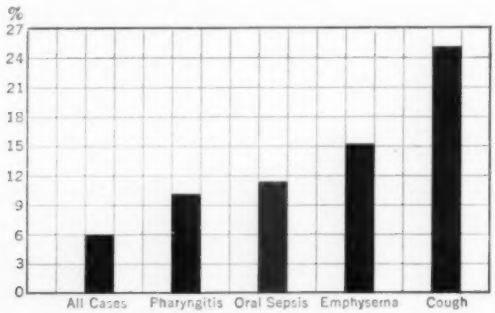

FIG. 2.—The percentage incidence of postoperative respiratory complications in patients with certain pre-operative conditions diagnosed.

The significance of the preoperative respiratory conditions of patients operated upon is evident in Fig. 2. In this series 6% of all cases anesthetized developed some minor or major respiratory complication following operation. Those patients having pharyngitis, acute or chronic, before operation, showed a total incidence of more than 10% of postoperative respiratory complications. If oral sepsis was present, the incidence was nearly double that of all cases, while in cases having a cough, over 25% had the postoperative convalescence complicated by some respiratory abnormality.

A comparison of the complications following the use of various agents is shown in Fig. 3, and the different complications for these agents are listed in Table 2. That fewer complications would follow

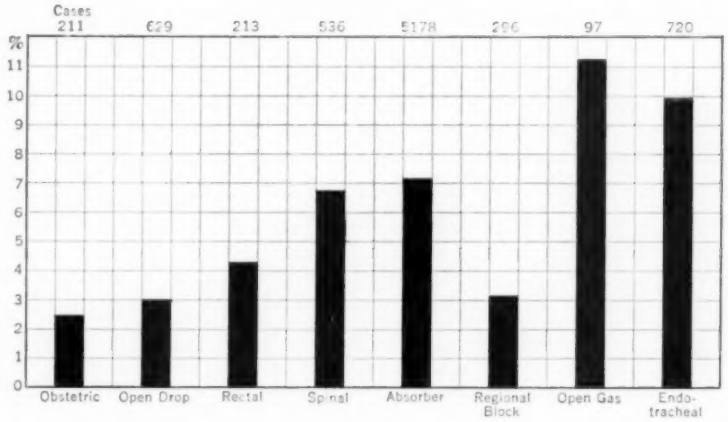

FIG. 3.—The number of anesthesias with each agent and the comparison of the post-operative respiratory complications represented graphically in percentages.

the use of nitrous oxid was expected since that agent was used in obstetrical analgesia, in dental extractions and in many superficial operations. Tribromethanol was used almost exclusively in good risk patients for ocular surgery, and was given only 213 times.

TABLE 2.—COMPLICATIONS WITH EACH AGENT.

	N_2O, %	C_2H_6, %	Ether, %	C_2H_6, %	Proc., %	T.B.E., %
None	94.50	86.10	92.20	93.50	92.00	94.30
Pneumonia, lobar and bronchial	0.31	0.30	0.24	0.41	0.72	0.47
Pneumonia, hypostatic	0.10	0	0.30	0.03	0.38	0
Collapse, partial	0.21	0.61	0.43	0.16	0.12	0
Collapse, massive	0	0.10	0.30	0.12	0	0
Bronchitis	0.10	0.38	0.51	0.28	0	0
Laryngitis	2.40	2.00	1.80	1.90	0.84	1.80
Cough	2.40	6.40	6.20	3.60	5.16	2.30
Hiccough	0.10	0.38	0.80	0.28	1.07	0
Obstruction, upper respiratory	0.31	0.71	0.90	0.22	0.12	0
Rhinitis	0.41	0.61	0.51	0.19	0.48	0.47
Pleurisy	0.21	0	0.30	0.12	0.38	0

A comparison of the seriousness of the risks done with each agent is shown in Table 3. Anesthetic risks were classified as follows: "Emergency" patients who, previous to operation, had insufficient clinical examinations to permit a feasible estimation of the risk. "A"—Patients in excellent physical condition to undergo a minor operation. "B"—Patients in good physical condition who are to

undergo a serious operation, or those whose physical condition is impaired but a minor procedure contemplated. "C"—Patients who have a definite organic lesion or lesions other than that for which a serious operation is to be undertaken but which should not be expected to be fatal in the near future. "D"—Patients with a very serious physical handicap which might prove fatal in the not distant future, and are to have an operative procedure of an extremely serious nature. "DD"—Patients whose condition is desperate, where the possibility of death at operation is not remote, and without operation is likely. Table 3 shows that the larger per cent of the serious risks were done with cyclopropane, ethylene and ether in the order named.

TABLE 3.—ANESTHETIC RISKS WITH EACH AGENT.

Agent.	Emergency.	A.	B.	C.	D.	DD.
N_2O	32.7	11.7	35.9	16.0	3.2	0.41
C_2H_4	16.8	6.9	39.4	28.9	6.9	1.02
Ether	17.2	10.7	39.7	25.5	6.0	0.83
C_3H_8	16.4	4.5	33.2	35.6	8.7	1.50
Procain	5.7	5.2	41.1	44.5	2.9	0.48
Tribromethanol	16.2	5.6	50.2	21.1	6.8	0
Total	17.5	8.4	36.8	29.6	7.2	0.49*

Figure 4 compares the complications for the various risks. Two-thirds of the patients were in the "B" and "C" classification. Very few were in the "DD" group (Table 3).

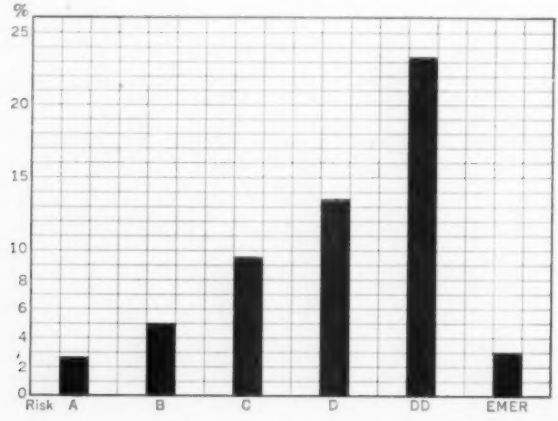

FIG. 4.—Postoperative respiratory complications found in different surgical risks.

The anesthetic agents employed for the different surgical procedures are shown in Table 4. General surgery, including thyroid

and central nervous system operations, was more often accomplished with cyclopropane, ether and ethylene. A large per cent of nose and throat operations were done with ether, since tonsillectomies for children are included. In each case, the agent producing the more profound degree of narcosis is credited as the anesthetic for that operation. A nitrous oxid-ether sequence was considered an ether anesthesia. Likewise if ether was used to facilitate tracheal intubation and the anesthesia maintained with ethylene or nitrous oxid, the case was recorded as an ether anesthesia. If tribromethanol was used and supplemented by a gaseous agent, the former received credit for the case.

TABLE 4.—AGENTS USED FOR DIFFERENT SERVICES.

Operation.	Agents.								
	N_2O.	C_2H_4.	Ether.	$CHCl_3$.	C_3H_6.	Proc.	T.B.E.	Others.	Total.
General surgery	241	370	456	9	1190	413	9	16	2704
Orthopedic	134	279	289	1	729	44	0	2	1478
Gynecologic	272	188	210	0	744	8	5	76	1503
Obstetric	211	33	10	0	62	1	0	0	317
Genito-urinary	23	43	42	0	214	341	6	0	669
Ear, nose and throat	10	16	407	3	66	0	1	2	505
Eye	16	2	13	0	33	0	185	2	251
Plastic	7	18	166	1	75	1	4	0	272
Dental	39	22	98	0	66	1	0	40	266
Others	0	0	1	0	9	1	0	0	11
Anesthesia only	4	3	14	0	15	9	3	1	49

Figure 5 compares the percentage incidence of respiratory complications following the use of various anesthetic techniques. It might be expected that few complications would follow the inter-

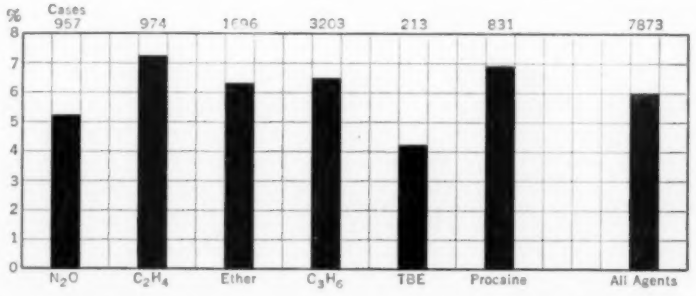

FIG. 5.—The percentage incidence of postoperative respiratory complications following the different anesthetic methods employed. The number of cases anesthetized by each technique is shown.

mittent use of gas in obstetrical cases and this was found to be true. The open drop ether anesthesias were, in more than 60% of the

cases, done for tonsillectomies in children. The technique was not used for abdominal surgery and never selected when a serious risk was undertaken. The rectal technique was used for tribromethanol anesthesia, and in more than 90% of the cases, for ocular surgery. Spinal technique was more often chosen for genito-urinary surgery. Some lower and upper abdominal cases were anesthetized by intradural injections, but the technique was avoided in celiotomies if the patient was considered more than a "C" risk. Patients anesthetized by regional block presented, in a large per cent of the cases, serious circulatory or other complications, as for example, transurethral prostatic resections in aged men with advanced circulatory path-

TABLE 5.—CASES ANESTHETIZED BY THE ENDOTRACHEAL TECHNIQUE.

Surgery.	Total cases.	Risks.					
		E.	A.	B.	C.	D.	DD.
Dental	160	34	15	75	35	1	0
Ear, nose and throat	25	6	1	7	11	0	0
Plastic	86	15	1	49	20	1	0
Eye	12	2	0	7	3	0	0
Kidney	6	0	0	2	3	0	1
Gynecologic laparotomy	26	1	1	13	12	0	0
Craniotomy	63	2	0	0	18	41	3
Thyroid	12	2	0	2	5	2	1
Thoracic	8	0	0	0	1	7	0
Gall bladder	57	5	0	5	43	4	0
Gastro-intestinal	112	4	1	13	46	46	0
Hernia	15	1	0	5	9	0	0
Rectal	12	0	0	1	4	7	0
Laminectomy	29	2	1	1	16	5	4
Bone and joint	26	5	1	8	11	1	0
Others	73	7	2	23	30	9	2
Total cases	722	86	23	211	267	124	11
Per cent of total cases		11 9	3 2	29 2	36 9	17 1	1 5

ology. The remainder were minor operative procedures and rectal operations. Open gas technique (mask with exhalation valve and partial rebreathing) was not often used. It was never selected for serious operations. The incidence of complications may be unfair to this technique since the series is so small. Carbon dioxid absorption technique[2] was used for the majority of administrations. When endotracheal intubation is to be done, the tracheal airway merely replaces the face mask in the absorption technique. Endotracheal intubation is rarely used for other than serious risks except in intraoral surgery and exodontia. Surgery of the central nervous system, gastro-intestinal tract and gall bladder comprise the major-

ity of the cases. That the more serious and complicated surgical procedures are accomplished with endotracheal anesthesia is evident in Table 5 which lists the surgery, number of cases, and risk for that technique.

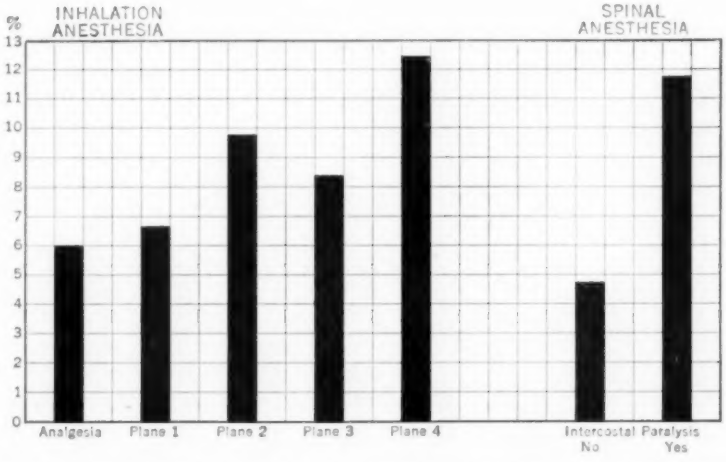

FIG. 6.—Percentage incidence of postoperative respiratory complications for the different planes of anesthesia. In spinal anesthesia the cases with paralysis of the intercostal muscles are compared with those where no such paralysis occurred. Regional anesthesias other than spinal block are omitted.

That the degree of narcosis is a factor effecting postoperative morbidity is indicated in Fig. 6. Stages of anesthesia after the classification of Guedel were used.[3] The planes shown in the graph are of the third stage. When using cyclopropane, the differentiation of Planes 3 and 4 was impossible. The latter plane of anesthesia was then considered to be that degree of narcosis where respiration was entirely passive or accomplished by the anesthetist. This corresponds to Stage 4 in Guedel's classification. The most profound degree of narcosis during the operation was considered as the plane of anesthesia for that case. Planes 1 and 2 were, of course, more often used for superficial operations, but many serious procedures such as central nervous system, thyroid and kidney operations were invariably done with this lighter anesthesia. Although Planes 3 and 4 were more often used for abdominal surgery, there were many of these operations accomplished in Plane 2. The individual preference of the surgeon was most often the anesthetist's guide to the depth of anesthesia required. When subarachnoid block was accomplished without disturbance of intercostal activity, the per cent of postoperative respiratory complications was less than one-half that found when the anesthesia produced intercostal muscle

paralysis. In the latter group, however, were operations inlvoving the upper abdomen.

Figure 7 represents a consideration of the influence of the operating time on respiratory sequellæ. Fifteen per cent of the nitrous oxid anesthesias, 30% of those with ethylene, 32% with ether and 45% with cyclopropane were for 60 minutes or more. Age and sex influenced the incidence of morbidity. Males developed some respiratory complication more often than females, the ratio for 1 year being 1.3 to 1. Infants under 1 year had fewer complications than any age group while adults suffered most often.

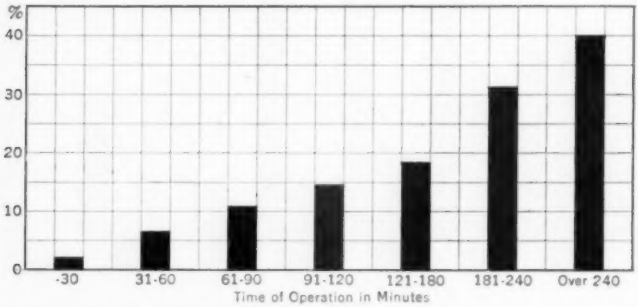

FIG. 7.—All operations were grouped according to the duration. The occurrence of postoperative respiratory complications for each group is graphically represented in percentages.

The statistics in Table 6 were of particular interest to the anesthesia staff since the postoperative morbidity for the individual anesthetists was compared. The contention that the ability, train-

TABLE 6.—COMPLICATIONS FOR INDIVIDUAL ANESTHETISTS COMPARED.

Anesthetist.		Collapse.		Pneumonia.		All respiratory complications.	
No.	Cases.	Ether.	C_3H_6	Ether.	C_3H_6.	Ether.	C_3H_6.
1	934	1.30	0.36	0.77	0.54	7.75	9.2
2	716	1.14	0.00	0.72	0.68	12.70	6.8
3	399	3.60	0.55	0.92	1.10	12.30	9.9
4	655	0.72	0.58	0.72	0.30	8.70	6.1
5	762	2.50	0.33	1.80	0.67	17.80	9.9
6	615	0.85	0.20	0	0.40	2.60	6.0
7	296	0	0	2.40	1.50	9.70	8.6
8	147	0	0	0	0.90	5.50	8.1
9	273	2.80	0.42	0	0.42	5.50	7.1

ing and experience of the anesthetist is the most important factor influencing anesthetic morbidity and mortality is not disproved by these data. In the table, Anesthetist 5 had the larger experience

and was assigned a large number of serious and difficult cases. Many of his anesthesias were given by medical students under supervision. Maintenance and recovery were not always adroitly consummated and this is evident from the data. Anesthetist 1 had more training than any other except 5. Many grave risks were allotted to him; 2, 3, and 6 had a similar amount of training. They were assigned routine cases. Anesthetists 4, 7, 8 and 9 had the least clinical work, but were given good risk cases that were not technically complicated. The results for ether and cyclopropane anesthesias are recorded. Although this table contains data concerning all respiratory complications and specifically pneumonias and collapse, comparable results were registered in the incidence of nausea and emesis and circulatory and other complications.

TABLE 7.—DEATHS FROM RESPIRATORY CAUSES IN VARIOUS SERVICES.

Surgical service.	Total cases.	Respiratory deaths.	
		No.	Per cent.
Orthopedic, minor	889	1	0.1
Herniorrhaphy, ventral and inguinal	407	2	0.5
Vaginal operation	933	2	0.2
Abdominal, lower	992	7	0.7
Ophthalmology	254	1	0.4
Plastic	174	1	0.4
Urology	588	6	1.0
Thoracic	194	6	3.1
Orthopedic, major	578	2	0.4
Ear, nose and throat	494	3	0.6
Abdominal, upper	476	8	1.7
Central nervous system	95	8	8.4
Rectal	235	1	0.4

TABLE 8.—RESPIRATORY DEATHS.

Total cases anesthetized	7874
Total deaths (all causes)	293 (3.72%)
Respiratory deaths	47 (0.59%)

Cause of respiratory deaths.	No.	N_2O.	C_2H_4.	C_3H_6.	Ether.	Proc.	T.B.E.
Pneumonia	31	2	5	9	11	3	1
Collapse	3	0	0	1	2	0	0
Embolus	4	0	0	1	1	2	0
Others	9	3	2	1	3	0	0
Total deaths	47	5	7	12	17	5	1
Total cases	7874	957	974	3103	1696	831	213

Time of death.	O.D.	1–3 P.O.D.	4–7 P.O.D.	2d wk.	Later.
Pneumonia	0	1	8	5	16
Collapse	0	1	1	1	0
Others	1	5	3	2	3
Total	1	7	12	8	19

In Table 7, the respiratory mortality for the series is recorded with the type of operation after which deaths occurred. The cause and time of death as well as the agent used is shown in Table 8. The group listed as "Others" includes aspiration of vomitus, foreign body, pulmonary edema, suffocation, and an accident.

Comment and Summary. It is of course impossible to give in detail all the minor and major respiratory complications found following 7874 operations. Primary attention has been given to anesthesia as contributing to the postoperative morbidity. Although a relatively small number of cases is reported, the data indicate several factors that merit consideration if such morbidity is to be reduced.

The marked seasonal variation is contingent upon the prevalence of respiratory diseases in the population outside the hospital. Other factors appear of less importance. It has been found advisable in this hospital during the months with a high incidence of respiratory infections to omit certain elective operative procedures, particularly plastic operations upon infants.

The presence of any respiratory tract infection, even mild pharyngitis or oral sepsis substantially increases the incidence of postoperative respiratory infections.

The influence of the anesthetic agent was not marked in this series. A careful selection of agents was practiced and comparable morbidity results secured with each.

Anesthesia technique was a more important factor but the incidence of complications more nearly paralleled the surgical procedure involved. When using intermittent analgesia for obstetrics and open drop for tonsillectomies, complications were rare.

The pre-operative risk classification gave the most accurate index of postoperative morbidity expectancy. The increase in respiratory complications was in direct proportion to the seriousness of the risk.

The degree of narcosis distinctly affected the percentage of complications. Evidently surgical procedures that can be well executed with first plane anesthesia should not have more profound narcosis. The training and skill of the individual surgeon will be the determining factor in the degree of narcosis required. Spinal anesthesia without intercostal muscle paralysis accounted for less than one-half as many complications as did the same procedure when the intercostal muscles were paralyzed.

The most striking influence upon postoperative respiratory complications was shown by the duration of operation. Whereas operations lasting 1 hour or less have a morbidity incidence less than the average for the group, the ratio for procedures requiring a longer time increases markedly. When the duration was 1 to $1\frac{1}{2}$ hours, the respiratory complications doubled those of 1 hour. When 2 hours were needed, the percentage of complications was more than 3 times that of 1 hour. In procedures lasting 3 hours, more than

31% of the patients had some respiratory complication. The group requiring more than 4 hours had the highest incidence of respiratory complication. Despite the seriousness of the longer surgical manipulations and the grave risks encountered in the majority of them, duration of operation alone appears to be a definite factor influencing respiratory morbidity.

That the ability, training and experience of the anesthetist modifies morbidity is well shown in these statistics. Teaching students and training anesthetists will be accomplished by an increase in postoperative complications.

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THE LAG PHASE IN EARLY CONGENITAL OSSEOUS SYPHILIS.

A ROENTGENOGRAPHIC STUDY.

BY NORMAN R. INGRAHAM, JR., M.D.,

ASSISTANT INSTRUCTOR IN DERMATOLOGY AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA; ASSISTANT PHYSICIAN TO THE PRENATAL CLINIC, DEPARTMENT OF GYNECOLOGY AND OBSTETRICS, PHILADELPHIA GENERAL HOSPITAL, PHILADELPHIA, PA.

THE value of any diagnostic procedure depends primarily upon its specificity, upon the relative frequency of its occurrence as compared with the total incidence of the disease in question, and upon the time interval necessary for its development after the morbid state is produced. Roentgenologists are universally agreed that the osteochondritis and periostitis which characterize infantile congenital syphilis can, in their typical forms, be confused with no other osseous lesion, and it is the experience of most that nearly 100% will develop bone changes diagnostic of this disease at some time within the first 6 months of postnatal life.[1–6] On the other hand, there seems to be no working criterion by means of which it is possible to determine exactly when the lesions in question are likely to appear in any given case and, since roentgenographic examination is a relatively expensive procedure, it is ordinarily impractical to make repeated Roentgen ray studies until the positive changes finally make their appearance, or until the presence of the disease is satisfactorily ruled out by their failure to develop. An attempt to establish the importance of some of the factors causing these individual variations may prove useful for developing

a rational and at the same time economical approach to the roentgenographic diagnosis of infantile congenital syphilis.

Most roentgenologists and pathologists who have studied the problem of early congenital bone syphilis have been impressed with the fact that the osteochondritis occurring in the metaphyseal growing centers of the bones of syphilitic infants is a phenomenon of fetal and of early postnatal life, and that periostitis in these cases, seldom present at the time of birth, is ordinarily at its height from the second to the fifth months of extrauterine life.[3, 7–10] Péhu, Policard and their associates[4, 5, 11] have especially insisted upon this classification. Exceptions to these general tendencies are common, however, and it is not especially unusual to find syphilitic periostitis in a fetus stillborn at or near term,[5, 12] nor is it uncommon for a syphilitic infant to have roentgenographically normal bones at the time of birth, only to develop diagnostic osseous lesions some few weeks or months thereafter.[3, 8]

The comparative ease with which spirochetes are demonstrated in the syphilitic placenta[13] and in the organs of infants which succumb to this infection[14, 15] would indicate that fetal syphilis is a more virulent disease than is ordinarily encountered in adult life. Whether this massive infection is the result of the repeated transfer of spirochetes from the maternal to the fetal circulation in the placenta over a period of months, whether it arises from rapid multiplication of the microörganism because the resistance of the embryo is low, or whether it is attendant on other circumstances of fetal development, it is probable that these factors just mentioned, since they affect all embryos similarly, have less to do with determining when the bone lesions will appear than has the actual time in intrauterine life in which the infection takes place. The fact that the offspring of syphilitic mothers are ordinarily inaccessible to study for some weeks or months after they have become diseased, has left the question of the duration of the disease in them at the time of birth largely a matter for conjecture. In addition, there is obviously a latent period from the time of spirochetal invasion until the impairment of bone development by the action of these microörganisms at the temporary zones of calcification has become sufficiently marked to affect the roentgenograph. An attempt to determine, as accurately as possible, this lag phase is the primary object of this study. For it is self-evident that if the latent period from the time of spirochetal invasion until the bone lesion becomes roentgenographically manifest is known, the approximate duration of the syphilitic infection in the child may be estimated with a reasonable degree of certitude. We have endeavored to attack the problem from several angles, checking one result against another in an effort to determine whether they coincided sufficiently to warrant any definite conclusions. Since the living human fetus cannot be studied adequately prenatally, the evidence brought

forth must be, in part at least, inferential, if the question is to be clarified at all.

In this connection, attention should be directed toward the work of Alexander[16] and Harris,[17] Klaften and Priesel,[18] the greater part of which we have been able to confirm. The former 2 observers pointed out that it is possible, in certain instances at least, where syphilitic osteochondritis is present at the time of birth, to estimate the approximate month in fetal life at which the first recognizable bone lesion appeared, by assuming that impaired osseous development results from then until the time of birth and by measuring the width of this bone scar on the diaphysis (Fig. 6). The latter investigators attempted to estimate the duration of the bone lesion at the time of birth in the offspring of partially treated syphilitic mothers, utilizing the apparent fact that, if the child is infected before prenatal treatment is commenced, the bone development proceeds more or less normally after the onset of therapy, leaving bands of sclerosis, vestiges of the antecedent active infection on the shaft of the bones at varying and easily measured distances from the metaphyses.

Material. Our material consists of 252 complete roentgenographic studies performed on the offspring of 131 syphilitic pregnancies which occurred in the Philadelphia General Hospital between December 1, 1933, and June 15, 1935. Each mother was carefully studied from the standpoint of this disease prenatally and postnatally, and the majority of the children were followed for a matter of several months, or at least long enough to confirm the roentgenographic studies by clinical and blood serologic examination. Few of the children received any antisyphilitic therapy during the period of observation, so the roentgenographic picture obtained resulted for the most part from the syphilis alone and was not the outcome of the combined changes produced by syphilis and therapy. The group of cases followed by serial studies is further highly selected in that only the infants who received little or no prenatal therapy and whose mothers were proven to have active early syphilis with strongly positive serologic reactions were considered. Accordingly, about one-half of the 258 syphilitic deliveries which occurred in the hospital in this period of time was thought suitable for the purposes of this study. The sole idea in thus selecting the cases was to obtain as high as possible a number of diseased children and thus of positive roentgenographs.

The Fetus is Apparently Infected in the Latter Half of Pregnancy. As a preamble to the report of the actual results obtained, it is of considerable interest and importance to note what can be gleaned from the literature regarding the earliest recognizable fetal bone changes as compared with the earliest demonstrated syphilitic spirochetosis. Clinical and pathologic studies have indicated that syphilitic miscarriage is uncommon, if indeed it occurs at all, prior

to the 16th week of pregnancy.[19] For instance, it has been shown that spontaneous abortion (*i. e.*, miscarriage prior to the 4th month) is of no greater frequency among syphilitic than it is among non-syphilitic mothers. Similarly, late miscarriage has a noticeably greater incidence among known syphilitic patients. Prenatal antisyphilitic therapy which, according to the best authorities,[20, 21] exerts its beneficent action principally by preventing the transplacental transfer of spirochetes and not so much by treating an already infected fetus, can assure the birth of a healthy infant in almost 100% of cases if it is continued throughout the latter half of pregnancy only.[22, 23, 24] Gräfenberg,[25] who has carefully studied the bacteriology of fetal syphilis and whose work has been confirmed by many European investigators and generally accepted,[7–10, 26] states that he could discover no embryo which contained spirochetes prior to the 16th week of fetal life.

Assuming then, as seems justified, that the earliest fetal infection dates from the beginning of the 5th lunar month, let us see when, in embryonal life, syphilitic bone changes can first be recognized roentgenographically. Fraenkel[12] was able to show a definite osteochondritis by this means in a 26 cm. fetus; Alexander[16] discovered early osseous changes in fetuses 26.5, 27.5 and 28 cm. in length. A 26 cm. fetus is in its 6th lunar month of intrauterine life, 21 to 22 weeks old.[27, 28] Syphilitic bone changes have, apparently, never been demonstrated roentgenographically in fetuses younger than this. According to Fraenkel's comprehensive studies,[12, 29] the fetal periostitis may begin to become evident roentgenographically in 42 to 43 cm. fetuses, namely, in those which are 32 to 34 weeks old. Harris', Alexander's, and Klaften and Priesel's studies with older stillborn fetuses or with living infants indicate that the earliest bone changes date from the 6th lunar month of intrauterine life. The presumptive evidence, therefore, would seem to indicate that osteochondritis becomes recognizable roentgenographically 5 to 6 weeks following fetal infection and that about 16 weeks are necessary for the development of a manifest early periostitis.

A Syphilitic Child Born of a Mother Infected Late in Pregnancy. Another method of determining the approximate period in intrauterine life in which the fetus is infected is by selecting for study mothers who are infected and who develop signs of primary or secondary syphilis in the later months of pregnancy. Spirochetemia is at its height at about the secondary stage of the disease, so that a pregnant woman who develops clinical early syphilis close to term will, presumably, infect her offspring very quickly and readily, if she is permitted to go untreated. That mother who acquires her disease closest to the time of birth of her child and whose offspring shows, at the same time, an early osteochondritis when delivered, will give a fairly accurate measure of the time required for this diagnostic sign to appear in the roentgenograph.

Of the 258 syphilitic deliveries which occurred in the Philadelphia General Hospital during the period of this study, 17 fall into this classification. They are summarized in some detail in Table 1. Two of the offspring were stillborn and 1 died in less than 24 hours; these were not studied roentgenographically. Of the living children, 5, those who had received considerable prenatal treatment, were clinically and roentgenographically normal; 2 of the infants were not adequately followed. The remaining 7, born 4, 9, 12, 15, 16, 18 and 23 weeks, respectively, after the onset of clinical symptoms in the mother, all showed syphilitic osteochondritis on their first postnatal Roentgen examination (Figs. 1 and 2). In Case 256, the mother had been infected for about 8 weeks only and the child, presumably, for something over a month before the roentgenograph was performed. This type of evidence, therefore, would indicate that about 5 weeks are necessary for the development of Roentgen-positive bone syphilis.

TABLE 1.—ROENTGENOGRAPHIC DIAGNOSIS IN INFANTS WHOSE MOTHERS DEVELOPED PRIMARY OR SECONDARY SYPHILIS LATE IN PREGNANCY. THE LAG PHASE IN THESE CASES IS SHOWN TO BE ABOUT 5 WEEKS.

No.	Type of syphilis in mother.	Date of onset of clinical symptoms in mother.	Date of delivery.	Child born.	Prenatal treat. (weeks).	Wassermann (At birth) Mat.	Wassermann (At birth) Cord.	Date appearance congenital bone syphilis.
49	Papular secondary	8/ /34	2/13/35	Dead	None	4+	4+	
64	Genital condylomata	1/ 9/34	3/19/34	Dead	4	4+	4+	
162	Papular secondary	7/ 5/34	10/ 6/34 (Lived less than 24 hrs.)	Alive	3	4+	4+	
20	Genital primary	8/10/34	12/11/34	Alive	10	Neg.	Neg.	Child not syphilitic
55	Maculopapular secondary	6/25/34	1/16/35	Alive	23	3+	Neg.	Child not syphilitic
62	Genital condylomata	6/ 7/34	11/12/34	Alive	10	4+	Neg.	Child not syphilitic
101	Maculopapular secondary	4/15/34	8/21/34	Alive	11	Neg.	Neg.	Child not syphilitic
213	Annulopapular secondary	1/15/34	6/13/34	Alive	11	4+	1+	Child not syphilitic
83	Genital primary Papular secondary	11/27/33	2/24/34	Alive	7	2+	Neg.	Not Roentgen rayed
119	Annulopapular secondary	9/24/34	3/ 3/35	Alive	7	Neg.	Neg.	Child not followed
256	Genital primary	4/15/35	5/13/35	Alive	None	1+	Neg. (Early osteochondritis)	5/20/35
21	Maculopapular secondary	3/15/34	4/14/34	Alive	None	4+	4+ (Early osteochondritis)	5/25/34
						Advanced periostitis		9/18/34
52	Maculopapular secondary	12/24/34	3/20/35	Alive	12	Neg.	Neg. (Osteochondritis)	3/27/35
102	Genital primary Annulopapular secondary	12/26/33 12/21/34	6/13/34	Alive	8	1+	Neg. (Osteochondritis)	6/20/34
						Advanced periostitis		9/25/34
188	Genital primary Papular secondary	8/24/33	12/23/33	Alive	6	Neg.	Neg. (Osteochondritis)	12/29/33
17	Genital primary	8/15/33	12/ 2/33	Alive	1	4+	Neg. (Osteochondritis)	12/8/33
160	Papular secondary	2/15/34	7/27/34	Alive	6	Neg.	Neg. (Osteochondritis)	8/2/34

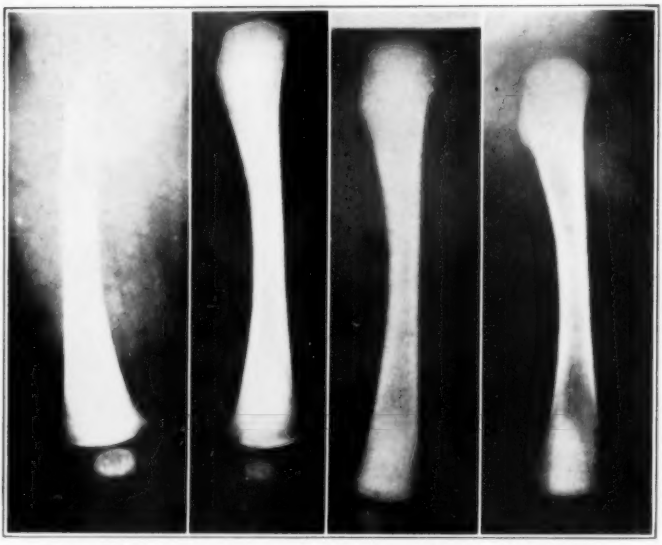
Osteochondritis Not Present at the Time of Birth Develops Postnatally. Further evidence can be obtained concerning this lag phase by selecting those cases in which a syphilitic child is born with no demonstrable osseous lesion, but in which Roentgen evidence of bone

involvement develops postnatally. This was true in the 16 cases in our series which are summarized in Table 2. All of these mothers had latent syphilis. Obviously, since about 20% of the offspring of untreated mothers with active syphilis fail to contract the disease,[23, 24, 30, 31] in spite of 9 months of indirect exposure to the mother's blood and tissues while they are *in utero*, infection of the embryo may occur right up until the time of delivery. A fetus infected before birth will develop bone changes sooner postnatally than the infant infected at the time of birth, the latter having the longest postnatal interval before osseous changes are demonstrable. Casazza[7] has pointed out that syphilitic osteochondritis is seldom seen after the 3d or 4th months of extrauterine life, but no effort, apparently, has been made to discover exactly how long after birth the earliest changes could be detected, though Schneider[8] had 1 case which showed a rather early metaphyseal lesion at the age of 2 months. The first 6 cases in Table 2 showed their early osteochondritic changes at 4 (4×), 5 and 6 weeks, respectively. This would indicate that it takes no less than 4 weeks and no more than 6 weeks ordinarily for the first bone changes to develop.

TABLE 2.—OSTEOCHONDRITIS NOT PRESENT AT THE TIME OF BIRTH BUT BONE CHANGES APPEAR LATER. DURATION OF TIME POSTNATALLY UNTIL THE DEVELOPMENT OF THESE OSSEOUS LESIONS. ALL CHILDREN BORN ALIVE OF MOTHERS WITH LATENT SYPHILIS.

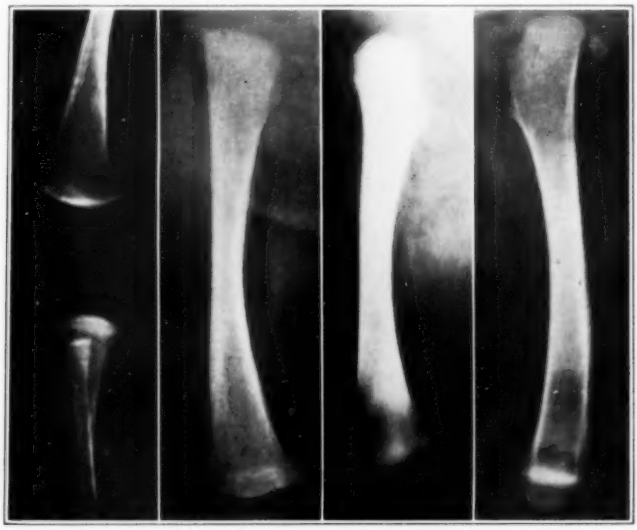
No.	Date of birth.	Date when roentgenograph became positive.	Weeks postnatally when positive roentgenograph was discovered.	Type of bone change.	Prenatal treatment (weeks).	Child's clinical symptoms.	Wassermann at time of delivery. Mat.	Cord.
72	7/25/34	8/28/34	4	Osteochondritis	3	None	1+	Neg.
109	7/22/34	8/21/34	4	Osteochondritis	1	Lymphadenopathy	3+	Neg.
121	12/ 4/34	1/15/35	6	Osteochondritis	2	Gen. lymph.	4+	2+
		2/19/35	10	Periostitis		Palp. spleen		
163	9/17/34	10/23/34	5	Osteochondritis	8	Snuffles	3+	Neg.
		11/20/34	9	Periostitis	.	Syphiloderm, palp. liver and spleen		
1	5/15/34	6/15/34	4	Osteochondritis	0	Snuffles	3+	Neg.
		10/ 9/34	20	Adv. periostitis	..	Gen. lymph.		
132	12/14/33	1/15/34	4	Osteochondritis	0	Snuffles	4+	?
		4/19/34	26	Adv. periostitis	..	Syphiloderm, palp. liver and spleen		
208	11/18/34	1/15/35	8	Early periostitis	16	Snuffles	4+	Neg.
211	5/23/34	7/17/34	8	Early periostitis	13	Snuffles, splenomegaly	1+	Neg.
232	9/ 1/34	10/30/34	8	Periostitis	4	Snuffles	Neg.	Neg.
147	1/23/35	3/26/35	9	Osteochondritis, periostitis	4	Snuffles	3+	Neg.
251	3/ 8/34	5/21/34	10	Periostitis	5	None	4+	4+
183	9/18/34	12/18/34	12	Osteochondritis, periostitis	13	None	1+	Neg.
61	7/ 6/34	10/ 4/34	12	Periostitis	7	None	4+	Neg.
181	2/13/34	5/22/34	13	Osteochondritis, periostitis	13	None	Neg.	Neg.
202	6/22/34	9/25/34	13	Periostitis	9	Snuffles	2+	Neg.
218	1/19/34	5/ 3/34	14	Periostitis	11	Child died, syphilis, 5/6/34	1+	3+

In Case 121 periostitis was demonstrated only 4 weeks after the osteochondritis became manifest. This may indicate that the latter change should have been recognized earlier, possibly even at the time of birth. Case 163 (Fig. 3) falls into a similar category, for here, although diagnostic bone changes did not develop until



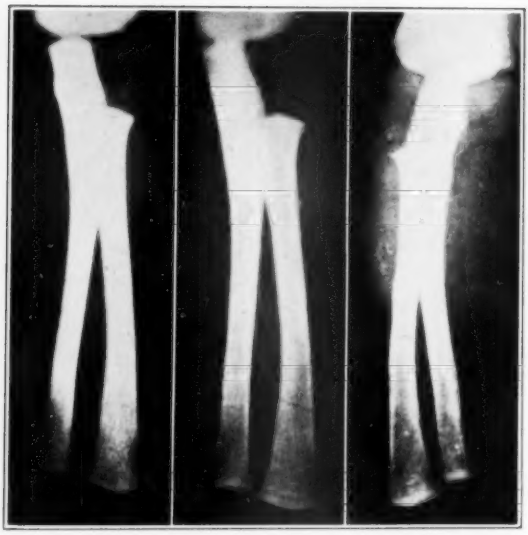
Case 256 Case 52 Case 188 Case 160

FIG. 1.—Early syphilitic osteochondritis in distal femoral metaphyses, at the time of birth, in infants whose mothers contracted syphilis late in pregnancy. Note the narrow band of sclerosis with slight submetaphyseal rarefaction in each instance.



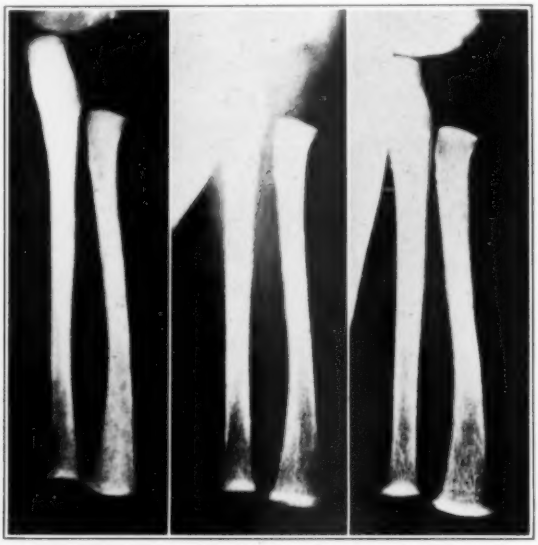
A *B* *C* *D*

FIG. 2.—Cases 21 (*A* and *B*) and 102 (*C* and *D*) showing early osteochondritis and later periostitis in femora; the mothers contracted syphilis late in pregnancy. The osteochondritic change shown in *A* is when the infant was 5 weeks old. Note marked metaphyseal sclerosis in all the long bones shown, with beautiful zone of submetaphyseal rarefaction and second zone of increased density shown in proximal tibia. *B* is at the age of 5 months with marked periostitis on the outer aspect of the diaphysis. Diaphyseal rarefaction is clearly shown in *C* at 6 days and *D* at 3 months. The latter shows, in addition, periostitis.



A B C

FIG. 3.—The development of syphilitic osteochondritis and periostitis postnatally. *A* shows the radius and ulna at 6 days with no more than normal metaphyseal sclerosis; *B*, the child is 1 month old. There is a definite zone of sclerosis in the distal radial and ulnar metaphyses with a zone of submetaphyseal rarefaction and a second poorly defined band of sclerosis. *C*, the metaphyseal sclerosis has increased and there is an early periostitis, best seen on the inner aspect of the shaft of the ulna and on the outer aspect of the shaft of the radius.



A B C

FIG. 4.—Case illustrating the fact that it takes several weeks for syphilitic osteochondritis to reach its height. *A*, when the child is 6 days old, the metaphyseal sclerosis is scarcely discernible; *B*, at the age of 1 month, the band has greatly increased in width, while *C*, at the age of 2½ months, there is in addition some flaring of the metaphyses with a tendency toward spur formation.

A *B*

FIG. 5.—The time interval between the appearance of syphilitic osteochondritis and syphilitic periostitis in the roentgenograph. This is Case 190 which showed early osteochondritis in the distal femoral metaphysis, *A*, at the time of birth. By the age of 11 weeks, *B*, the metaphyseal sclerosis has become more marked and an early but definite periostitis is present on the outer aspect of the diaphysis.

A *B*

FIG. 6.—Marked diaphysitis in the femur and tibia produced by prolonged action of the syphilis spirochete in the temporary zones of calcification. In *A*, the infant was 6 days old, the syphilitic infection dating in all probability from the 6th month of pregnancy. *B*, a similar picture in a 10-month-old infant. This is Case 188, the early osteochondritis of which is shown in Fig. 1. The infant received a small amount of treatment postnatally but was lost sight of for several months, to return for observation with the peculiar osseous picture illustrated.

the infant was 5 weeks old, there was a questionable osteochondritis at the time of birth, indicating that the infection *in utero* had probably occurred earlier than we had originally calculated. The fact that it took Cases 1 and 132 16 and 22 weeks, respectively, to develop moderately advanced periostitis would indicate that several months are usually consumed in forming this Roentgen picture. More accurate information can be obtained concerning this latent interval from a careful study of the remaining cases in Table 2 and from those summarized in Table 3, in which osteochondritis was present at the time of birth but in which the lapse of time necessary for the development of periostitis has been accurately determined.

The Latent Interval Necessary for the Development of Syphilitic Periostitis. The last 10 cases in Table 2 summarize the instances in which early periosteal changes were discovered postnatally, no bone changes being present in the roentgenograph at the time of birth. The longest time interval necessary for the development of an early periostitis will indicate the child infected closest to the time of birth, in this series the latent interval being 12 to 14 weeks. In other words, periostitis appears, presumably, between 3 and 4 months after the child is diseased.

TABLE 3.—OSTEOCHONDRITIS PRESENT AT THE TIME OF BIRTH. LAPSE OF TIME UNTIL PERIOSTITIS DEVELOPED; UNTREATED CASES.

No.	Date of birth.	Date when periostitis was discovered.	Weeks postnatally that periostitis developed.	Prenatal treatment (weeks).	Child's clinical symptoms.	Wassermann at time of delivery. Mat.	Cord
117	8/ 5/34	9/27/34	7	1	Child died cong. syph., 5/3/35	4+	Neg.
129	8/18/34	10/ 9/34	8	2	Gen. lymph., palp. liver and spleen	1+	Neg.
10	1/20/34	3/19/34	8	1	None	3+	Neg.
247	4/11/34	6/ 7/34	8	8	Snuffles, syphiloderm, gen. lymph.	3+	Neg.
118	1/23/34	3/22/34	8	1	None	Neg.	Neg.
35	1/13/35	3/21/35	9	None	Pseudoparalysis of Parrot	Neg.	Neg.
137	10/ 1/34	12/ 9/34	10 (early)	11	None	4+	Neg.
190	1/30/34	4/23/34	11 (early)	9	Gen. lymph., hepatomegaly	2+	Neg.
112	1/29/34	4/23/34	11 (early)	8	None	1+	Neg.
82	2/28/34	6/12/34	14 (definite)	2	Snuffles, gen. lymph., splenomegaly	Neg.	Neg.
28	12/14/33	4/ 2/34	15 (advanced)	8	None	4+	Neg.

Now turning to Table 3, and assuming again that the longest time interval before the development of periostitis indicates the child infected closest to the time of birth, and excluding Cases 28 and 82, in which the periostitis when discovered was moderately advanced, the longest osteochondritic-periosteal interval is 10 to 11 weeks (Figs. 4 and 5). This indicates again that periostitis develops some 2 to 3 months after the osteochondritis appears and some 4 months after the child is infected.

These results coincide rather well with the ideas portrayed in the

theoretical discussion which preceded the description of our actual findings: namely, if syphilitic fetuses stillborn at or near term comprise those embryos which have been infected earliest in the pregnancy, the periostitis which occurs not uncommonly in such offspring would indicate that they become diseased ordinarily about 4 calendar months before birth or in the 5th month of intrauterine life. Since the children born alive, on the other hand, do not ordinarily show periostitis until several weeks postnatally, such infants probably become diseased in the still later months of pregnancy.

Summary. Even though it has been realized for some time that considerable information could be derived concerning the duration of an osseous lesion produced by congenital syphilis from a roentgenographic study of the extent of the impairment of bone development after the lesion first became detectable, the fact that the latent interval between the time of fetal infection and the development of the earliest demonstrable osteochondritic and periosteal changes was unknown, left the actual duration of the disease in the infant a matter largely for speculation. We realize that the extent of the lag phase may be, and in some instances probably is, governed by a number of interplaying factors, but we have been impressed, as have a few other workers who have studied congenital bone syphilis by means of serial roentgenographs, with the almost mathematical time precision with which these lesions become manifest. By a study of the time interval alone, the majority of the individual variations found in comparing one case with another can apparently be explained; the few exceptions are probably caused by the addition of other elements, the relative importance of which remains to be determined (Fig. 6). Nonetheless, we feel that we may assume, with a reasonable degree of accuracy, that syphilitic osteochondritis, all other things being equal, becomes roentgenographically manifest about 5 weeks after the fetus is infected, while syphilitic periostitis requires approximately 4 months to develop.

It should be apparent, therefore, that the roentgenographic diagnosis of congenital syphilis, to be of its greatest value, must rest upon the recognition of syphilitic osteochondritis, for, by the time periostitis has developed, the child has been infected for several months, usually exhibits clinical signs of the disease, and has ordinarily become seropositive.* A single roentgenogram performed when the infant is 6 weeks old should detect almost every case, though osseous lesions could be discovered sooner in many instances, were not repeated roentgenographic studies inhibited by their expense.

* The unreliability of the blood serologic test as an absolute diagnostic criterion of congenital syphilis in the first few weeks of life is well recognized. In an article entitled, "Roentgen Positive, Sero-negative Infantile Congenital Syphilis," soon to appear in the Am. J. Dis. Child., we have indicated the value of roentgenographic examination in these seronegative, and otherwise undiagnosable cases.

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THE MINOR BLOOD AGGLUTININS AND THEIR RELATION TO POST TRANSFUSION REACTIONS.

By William P. Belk, M.D., F.A.C.P.

INSTRUCTOR IN CLINICAL BIOCHEMISTRY, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

The minor hemagglutinins (the subgroup isoagglutinins; Landsteiner's irregular isoagglutinins and normal cold agglutinins; the pathologic cold agglutinin; and the rouleau forming property) have

been the subjects of several interesting studies.[1–9] Very little effort, however, has been made to determine their practical importance in relation to the transfusion of blood. Landsteiner and Levine[2] report 6 transfusions without reaction with bloods showing minor incompatibilities at 20° C. Manheims and Brunner[11] report a transfusion without reaction in an individual with autoagglutinin, and Sherman[11] records two such instances. Tiber[12] considers the intra-group incompatibilities insufficient to cause death. Kramer[13] recounts 10 cases of autoagglutination with a severe reaction in 1. Brewer[14] finds auto- and cold agglutinins the most frequent cause of incompatibility between patients' serum and donors' cells, and attributes reactions to them. Unger[15] noted sharp reactions when minor incompatibilities existed in the cross tests.

The sub-group isoagglutinins, the irregular isoagglutinins, and the normal cold agglutinins are not clearly defined, but merge one into the other, and are more frequently encountered and more active at low temperatures. Landsteiner states that practically all human sera agglutinate their own cells at 0° C. The pathologic cold agglutinin (autoagglutinin) does not differ clearly from the normal cold agglutinin, except that it is often of high titer and is associated with pathologic states. It seems reasonable to suppose that it is really the normal cold agglutinin increased in strength by some process of disease. At any rate minor agglutinins effective on the cells of the same individual and others of the same blood group (and on those of group 0) at low temperatures (10° to 0° C.), but not at high temperatures, comprise the majority of the minor agglutinins.

Autoagglutinin is characterized first by the fact that its property of clumping erythrocytes is entirely wanting at 37° C., but becomes increasingly effective as the temperature is lowered, being maximal at 0° C. At, or near, this temperature the agglutinin is fixed to the cells which become drawn into masses. As the temperature is elevated, the reaction is reversed, the agglutinin becoming detached and the cells "unclumped." This is a property of the serum, not of the cells. Furthermore, this is not a specific agglutinin, but one capable of acting on the red cells of many, possibly all, animals (panagglutinin). It is, nonetheless, a true agglutinin, being absorbable, and, apparently, not affected by lecithin. A few authors, however, believe it to be related to the rouleau forming property. This latter is not attributed to a true agglutinin, but rather to a physiochemical property of the serum related to surface tension. It is not removed by absorption, and is inhibited by lecithin. It does, however, draw cells into masses which can be confused with those of true agglutination.

The present study was undertaken after an experience in which failure to detect a strong autoagglutinatinin in a patient's serum resulted in a very severe post-transfusion reaction. A review of the

literature lent support to the idea that the minor agglutinins were probably of importance, although no conclusive evidence of this had been produced. I therefore decided to perform routine cross agglutinations according to the method here described with the hope of securing evidence bearing on this question.

Technique. The procedure here employed is as follows: Venous blood collected in sterile test tubes is allowed to clot at 37° C., or if previously chilled, is warmed to 37° C. After removal from the incubator, serum is promptly centrifuged and pipetted off to prevent any but slight chilling. The cells are collected in 1.5% sodium citrate in normal saline (or other suitable fluid) and washed twice in saline warmed initially to 37° C. These steps assure a maximum of autoagglutinin in the serum and its removal from the cells. On clean glass microslides ringed with a wax pencil the following mixtures are prepared: patient's serum and patient's cells, patient's serum and donor's cells, donor's serum and donor's cells, donor's serum and patient's cells. The suspensions are light, about 1%, as an excess of cells masks agglutination.[16] The slides are placed in the refrigerator (5 to 10° C.) for 30 minutes, then removed, one at a time, gently agitated and observed at once under the scope. Agglutination is recorded as from 0 to +4. A second observation is made after about 10 minutes at room temperature (or 37° C.) to note reversal of agglutination. The following is an example of the application of the technique from my protocols:

Patient's serum plus patient's cells +4
Patient's serum plus donor's cells +4
Donor's serum plus donor's cells 0
Donor's serum plus patient's cells 0

"Agglutination in patient's serum completely disappeared after 10 minutes at room temperature; no rouleaux. Diagnosis—strong autoagglutinin in patient's serum. Advise no more than 100 cc. blood be given at one time."

This technique detects incompatibilities due to both major and minor agglutinins, including the autoagglutinin. This latter is missed by the usual technique in which clots are allowed to become chilled, and serum-cell mixtures are incubated at room temperature.

During the period of the work here reported I was under the impression that microscopic inspection alone would clearly differentiate rouleau clumping, as claimed by Coca.[17] More recent experience has led me to believe, however, that this is not always a reliable method, for when autoagglutinin and the rouleau forming substance are present in the same serum, each appears to interfere with the characteristic behavior of the other. When in doubt, lecithin should be used, as suggested by Lattes.[18] One or two platinum loop-fulls of a rather heavy suspension in normal saline are mixed with the serum-cell suspension, which is then returned to the refrigerator for 30 minutes. Since lecithin was not used in this study, the reactions here recorded may represent some instances of rouleau clumping, although probably most are those of autoagglutination. I was also under the impression that a +4 slide reaction indicated an agglutinin of high titer. Again I have found, however, that such a reaction may be produced in undiluted serum with an

actual titer of no more than 1 to 4, or 1 to 8. Consequently, the +4 reactions here recorded do not necessarily indicate high titers.

This study of the minor blood agglutinins includes 161 sera from 130 patients, and 265 sera from as many presumably healthy donors (Chart I).

CHART I.—INCIDENCE OF AUTOAGGLUTINATION IN ILL AND HEALTHY SUBJECTS.

Agglutination.	Patients' Sera.	Patients' %	Donors' Sera.	Donors' %
0	61	38.0	104	39.3
+1	24	14.9	66	24.9
+2	39	24.2	69	26.0
+3	18	11.2	16	6.0
+4	15	9.3	4	1.5
Sub-groups	4	2.5	6	2.3
	161		265	

Four patients' sera and 6 donors' sera were found which contained no autoagglutinin, but which agglutinated the cells of one or more individuals of the same blood group. All of these were Group II sera and doubtless represented examples of the sub-group II. One such serum agglutinated the cells of 5 Group II individuals strongly (+3), of another weakly (+1), and of 3 others not at all.

Fifty-nine per cent of sera of both donors and patients had more or less power to agglutinate their own cells and the cells of others of the same group, while incompatibilities not associated with autoagglutination occurred in only about 2.5% of sera. Thus autoagglutination seems to account for the great majority of intragroup incompatibilities. While this type of reaction is equally common in donors and patients, and doubtless represents Landsteiner's normal cold agglutinins, the +3 reactions were twice as frequent, and +4 reactions 6 times as frequent in the sick as in the healthy subjects. This observation has its greatest interest in the implication that the normal cold agglutinins are often increased in titer by the processes of disease; and indicates that, in an average series of patients in need of transfusion, 1 in 5 will have in his blood an autoagglutinin of sufficient strength to make a post-transfusion reaction a probability.

Medical literature associates autoagglutinins (pathologic cold agglutinins) most often with hemolytic anemias, some forms of cirrhosis of the liver, paroxysmal hemoglobinuria, trypanosomiasis, and repeated transfusions (in rabbits). In this series the condition was most frequently associated with infections by hemolytic streptococci and staphylococci. One patient had had a ruptured ectopic pregnancy, and another was absorbing a large hematoma. It would appear, therefore, that the destruction of blood within the body is an important factor in the development of a strong autoagglutinin. This suggests the development of an antibody against the red cells of the same species, and even of the same individual. However,

this agglutinin is not a specific one, but one capable of acting on the red cells of many animals. Kramer suggests that auto-lipoid antibodies are developed in such instances, which react with the lipoids of the erythrocytes. Mino believes that under certain conditions of non-specific stimulation the body produces antibodies in excess, including the panagglutinin. Landsteiner's and Kettle's reports of weak cold agglutinins in practically every human blood supplement this idea. Belk[19] has furnished evidence of the same sort in a case of infectious mononucleosis.

It was hoped that this study would show conclusively that post-transfusion reactions are caused by, or are associated with, auto-agglutinins. In 209 transfusions, practically all by the citrate method, performed on 82 patients, there were 23 reactions (11%). Of these, 3 were apparently due to cardiac embarrassment, 1 to allergy, and 1 to incipient coagulation of the donor's blood. Two other reactions occurred with perfect cross tests, and seemingly should be attributed to technique, although every care was taken to avoid dirty apparatus, over-heating or chilling of the blood, and improperly made saline.[21] The desirability of a spray trap in the still was not known to me at the time this work was done, and this may have been a factor in the reaction. I believe, however, that conclusions drawn later are still justified. The typing sera were frequently checked, and in no instance was an error made in the blood group of patient or donor. This leaves 16 reactions (70%) for which there was no apparent cause except blood incompatibility due to autoagglutinins which were demonstrated prior to transfusion in 100% of this group. When individual cases are considered, the impression is obtained that smaller quantities of blood produced reactions in those with strong autoagglutinins, amounts of 110 and 115 cc. having been followed by reactions in the former, while no reaction occurred in any patient with a weak autoagglutinin unless 250 cc. or more, of blood was given. In a few instances repeated transfusions with increasing amounts of blood resulted in a reaction after the final and larger amount.

Proof positive of the relation between autoagglutinin and post-transfusion reaction was not developed, however, as reactions were not found to be more frequent in those with strong agglutinins. This observation is modified by the fact that the amount of blood given each individual was determined in advance by the degree of incompatibility as shown by the cross test, and patients whose serum showed +3 and +4 autoagglutination were either not transfused at all, or only with small amounts. I did not feel justified in giving such patients 400 to 500 cc. of blood. Had this been done, it is possible that a high per cent of reactions would have resulted in this group, and so clear proof of the rôle of the autoagglutinin in this connection have been furnished.

The suggestive evidence that agglutinins are productive of post-

transfusion reactions lies in these observations: 1, The incidence of reactions was quite low in this series in which the decision as to transfusion and the amount of blood to be given was based on the presence of autoagglutinin in the patient's serum; 2, the only apparent cause for 70% of the reactions was the presence of autoagglutinin in the patient's blood; 3, smaller amounts of blood seemed capable of producing post-transfusion reactions in patients whose serum contained a strong minor agglutinin than in those with a weak agglutinin; 4, in a few instances repeated transfusions with increasing amounts of blood resulted in a reaction after the last and largest amount only (Chart II).

CHART II.—HEMOLYTIC STREPTOCOCCUS SEPTICEMIA FOLLOWING ABORTION. AUTOAGGLUTINATION +4. MRS. M.

	Transfusion.	Reaction.
Morning	100 cc.	0
Noon	135 cc.	0
Evening	250 cc.	+

With the usual method of blood matching transfusion reactions are rather frequent, even when satisfactory donors are found. This had led to the practice of giving small repeated transfusions in the hope of avoiding these reactions. I am sure that there is little virtue in small transfusions as such, the chief reason for their use being the fact that large amounts are dangerous in some cases because of blood incompatibilities, or a weak circulation. Any adult in need of blood will usually need 400 to 500 cc., and it is less annoying to patient, physician and donor to give this in one operation, if this can be done safely. I feel that a method of donor selection which demonstrates minor agglutinins has this advantage, that it permits a rational, rather than an arbitrary selection of patients for small transfusions. It enables one to avoid over-doses of blood in those who probably can tolerate only small amounts (those with minor agglutinins), and under-doses in those who can safely be given 400 cc. or more. Very large quantities of blood in small repeated doses can, however, be given safely to patients with strong minor agglutinins, and if the first few injections be cautiously increased in amount, the tolerance of the individual can be determined without greatly overstepping it (Chart III).

Another practical consideration is this: Strong incompatibilities due to autoagglutinins (pathologic cold agglutinins) most often appear as a clumping of the donor's cells by the patient's serum. Now it is clearly shown that this is a property of the serum, not of the cells. Consequently, it is useless to test a succession of donors in the hope of finding one suitable, *when positive auto- and cross-tests* with the patient's serum show that the element of incompatibility lies there. Such a serum will similarly agglutinate the cells of all donors (with minor quantitative differences). What is

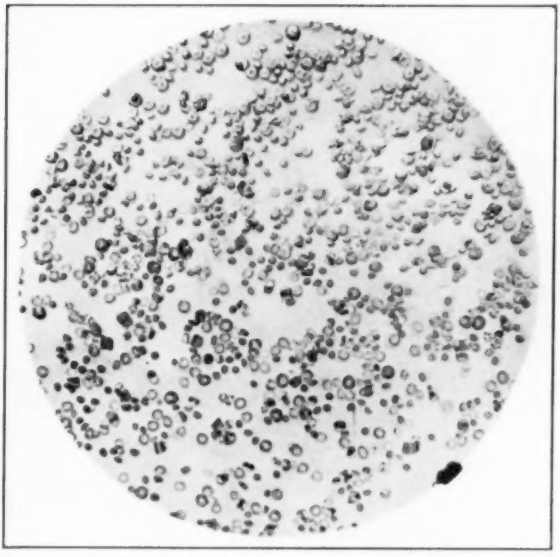

FIG. 1.—Serum and cells of an individual with autoagglutinin after 30 minutes at 20° C.

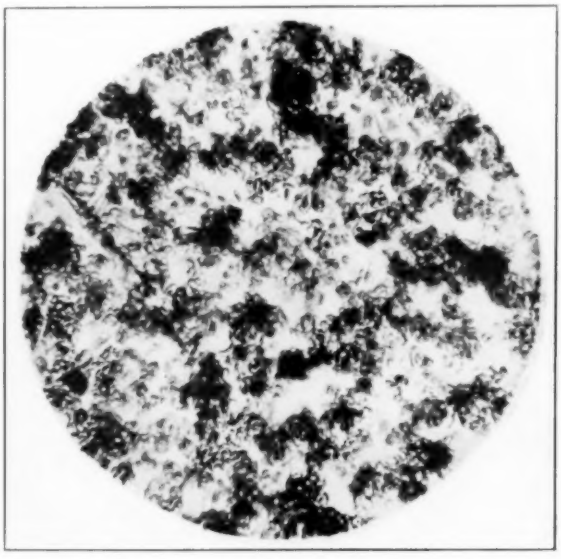

FIG. 2.—Serum and cells of same individual as in Figure 1 after 30 minutes at 5° C. showing how autoagglutination is demonstrated by chilling.

needed in such cases is not another donor, but another patient. Where the auto-test of the patient's serum is negative, but the cross-test positive, an error in blood grouping has probably occurred, or an irregular isoagglutinin is present. In such case, and when the donor's serum clumps the patient's cells, another donor will probably prove suitable.

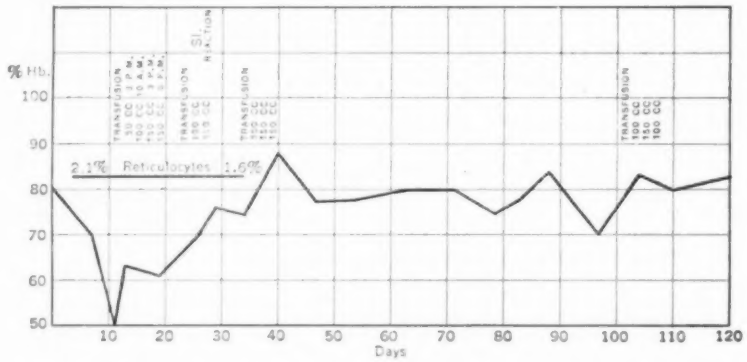

CHART III.—M. L.; aged 16. Acute osteomyelitis of knee (hemolytic Staphylococcus aureus.) Recovery. Strong autohemagglutinin in patient's blood. The first 4 transfusions were given within 30 hours.

The post-transfusion reactions in these 82 cases were characterized by fever of 1 to 2 degrees, or fever and chill, coming on 15 to 30 minutes after the transfusion, and lasting 10 to 15 minutes. Rarely was a reaction delayed as long as 1 hour. This observation is important, as it justifies repeating transfusions with no more than 3 to 4-hour intervals without fear of reactions overlapping. In a few cases, pain in the back and a feeling of constriction about the chest were complained of. In no case were purpura, hematuria, jaundice, or other delayed effects observed. The reactions, however, were severe enough to be very trying, and in weak individuals alarming. Atropin and adrenalin appeared to decrease the severity of the reactions. In this connection the possibility of the so-called citrate reactions is dismissed. Pharmacological studies of the effects of this drug[21] and practical experience,[22,23] to my mind, dispose of this possibility. Moreover, since this series includes 28 transfusions of 400 cc. or more with 2 gm. of citrate in each without any reaction, it is not logical to attribute reactions to citrate when used in smaller amounts.

This study, of course, has definite imperfections, since there are many factors which make it difficult to draw final conclusions. If the sera from a number of patients could be studied with the use of lecithin, by absorption, and by actual titration of the agglutinins, and the effect of transfusion noted on these patients, the relation

of the minor blood agglutinins to post-transfusion reactions would be definitely determined.

Conclusions. The autohemagglutinin (panhemagglutinin) is shown to occur frequently in the blood of patients needing transfusions, and to account for the majority of intra-group incompatibilities.

Evidence is advanced that a large per cent of post-transfusion reactions in carefully performed transfusions may be attributable to this agglutinin.

A technique of blood matching designed to detect autohemagglutinin and suggestions for transfusing in the presence of this agglutinin are given.

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THE EFFECT OF INJECTING CERTAIN ELECTROLYTES INTO THE CISTERNA MAGNA ON THE BLOOD PRESSURE.

By Harry Resnik, Jr., M.D.,
ASSISTANT IN MEDICINE,

M. F. Mason, Ph.D.,
INSTRUCTOR IN BIOCHEMISTRY AND RESEARCH ASSISTANT IN MEDICINE,

R. T. Terry, M.D.,
ASSISTANT IN PATHOLOGY, BALTIMORE CITY HOSPITAL,

Cobb Pilcher, M.D.,
ASSISTANT PROFESSOR OF SURGERY,

AND

T. R. Harrison, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, IN VANDERBILT UNIVERSITY, NASHVILLE, TENN.

(From the Departments of Medicine, Biochemistry and Surgery, Vanderbilt University, Nashville, Tenn.)

In the course of some observations on factors influencing the blood pressure of dogs we have tested the effect of urine extracts when injected into the cisterna magna. Certain extracts were found to have a marked pressor effect when administered in this way, but this effect was absent or reversed when these extracts in the same dosage were given intravenously. Since the pressor effect of intracisternal injection was not abolished by ashing the extracts and redissolving the residue in water, we were led to surmise that it was dependent on the presence in our extracts of inorganic salts. Accordingly, a study of the action on blood pressure of various electrolytes was undertaken.

Method. Most of the observations were made in dogs; a few goats were studied also. The animals were anesthetized with sodium pentobarbital ("nembutal"), 30 mg. per kg. of body weight, administered intravenously. If during the course of an experiment the animal became restless, small additional doses of the drug were administered. Blood pressure was measured with a mercury manometer connected with a cannula in the femoral artery. The cisterna magna was punctured with a 20-gauge needle connected with a tap which could be opened for removal or injection of solutions, or closed to prevent escape of fluid. Ordinarily, the needle and tap were left *in situ* for the duration of the experiment. In order to minimize changes in intracranial pressure injections were preceded by the removal of an amount of spinal fluid equivalent to the volume of the solution to be injected. When hypertonic solutions were administered, their effects were usually controlled by

the injection of equimolar sodium chlorid. Hypotonic solutions were made approximately isotonic by the addition of sodium chlorid.

In many of the experiments, analyses of the spinal fluid for calcium were made. For this purpose the Clark-Collip[1] modification of the Kramer-Tisdall[2] method was employed.

It was found that whenever respiratory paralysis occurred, a terminal rise in blood pressure, apparently due to asphyxia, was noted. In presenting the data only those effects are considered as significant which lasted for several minutes or longer after the injection; for injections of any liquid, even the dog's own spinal fluid, sometimes caused slight evanescent changes (in either direction) in blood pressure.

With these general methods a series of electrolytes was studied, including sodium, potassium, calcium, magnesium, lead, chlorid, sulphate, nitrate, oxalate, phosphate and citrate ions.

Results. A. Observations on Dogs. *Sodium Chlorid.* In an occasional dog a slight temporary rise in blood pressure might be produced by any intracisternal injection, even that of isotonic salt solution. Such effects were exceptional, lasted only a few seconds, and did not simulate the marked and prolonged effects produced by other ions. Increasing the strength of the sodium chlorid concentration was without effect until concentrations approaching molar were reached. Similar results were obtained with sodium sulphate. These observations indicated that the pressor effects which were obtained with much weaker dilutions of electrolytes cannot be ascribed to osmotic action.

Potassium Chlorid. When solutions ranging between 50 and 100 millimols per liter were injected in doses of 1 cc., a marked difference was observed between the effects of the first and of subsequent injections. The initial injection usually caused a decline in blood pressure. The second injection caused either a decrease —of lesser degree than that produced by the first—an increase, or a diphasic effect, the decline preceding the rise. The third and all subsequent injections usually caused an increase in blood pressure without a preliminary decrease, the effect being more or less proportional to the dose. Different dogs exhibited qualitative similarity but displayed considerable differences in the degree of response (Table 1 and Figs. 1 and 2).

The description applies only to doses within the range mentioned. Smaller amounts usually produced no effects when given initially but, in unusually responsive dogs, caused an increase in blood pressure after the animal had been previously "sensitized" by two or more preceding larger doses. When more concentrated solutions were used the initial injection usually caused a rise in blood pressure which might or might not be preceded by a temporary decline, and subsequent doses produced a marked rise.

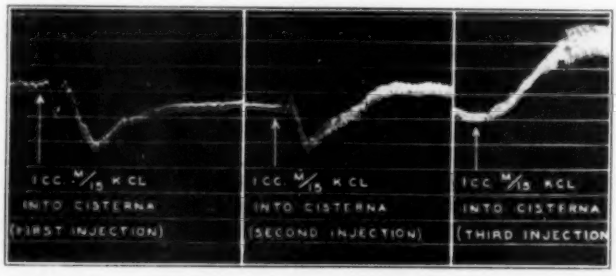
The duration of the pressor response was variable in different

dogs and was usually greater with larger doses. The effect always lasted several minutes and not infrequently persisted for ¼ hour. Fig. 2 illustrates a typical response, which endured for 18 minutes.

TABLE 1.—THE EFFECT ON THE ARTERIAL BLOOD PRESSURE OF DOGS OF THE INTRACISTERNAL INJECTION OF POTASSIUM CHLORID.*

Date, 1935.	Weight of dog, kg.	First injection.		Second injection.		Subsequent injections.	
		Solution injected, millimols per liter.	Change in blood pressure, mm.Hg.	Solution injected, millimols per liter.	Change in blood pressure, mm.Hg.	Solution injected, millimols per liter.	Change in blood pressure, mm.Hg.
Jan. 4	5.0	67	−42	67	+24	50	+18
						50	+20
14	9.0	100	−18	100	+18	50	+ 8
14	8.0	100	+64†	50	+56	33	+ 6
						50	+30
18	10.8	100	−48	100	+20	50	0
						67	+60
22	8.7	100	−18	100	+64	50	+40
23	8.1	100	−16	100	−12	100	+46
						50	+16
24	10.4	67	− 8	67	+52	50	+20
25	10.0	100	−38	100	+54	50	+34
26	11.5	100	−40	100	+88		
Apr. 5	19.5	67	−28	67	+10		

* The amount of fluid injected was 1 cc. in each instance.
† This increase was preceded by a diminution of 36 mm.

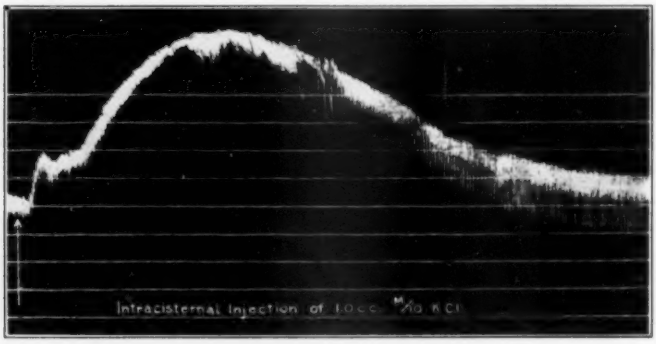


NOTE.—In all figures the curves run from left to right. The time intervals on the base line are 6 seconds. The distance between two adjacent horizontal lines represents 20 mm. of mercury. Arrows denote injections.

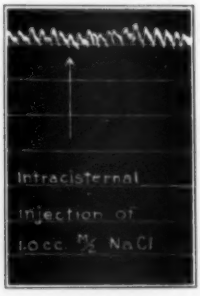
FIG. 1.—The three curves represent typical effects of repeated injections of potassium chlorid, the first injection causing a depressor response, the second producing a diphasic reaction and the third initiating a pressor effect.

Potassium chlorid solutions not only affected the blood pressure but other functions as well. Respiration was usually increased, the breathing often became stertorous, and the respiratory variations in blood pressure became more pronounced (Fig. 1). Sometimes the stimulation of breathing was noted following injections which did not affect the blood pressure. Restlessness, rigidity, opisthotonos

and muscular twitchings were frequently observed; convulsions were noticed only occasionally. The general picture was not unlike that of uremia as observed in patients.



A



B

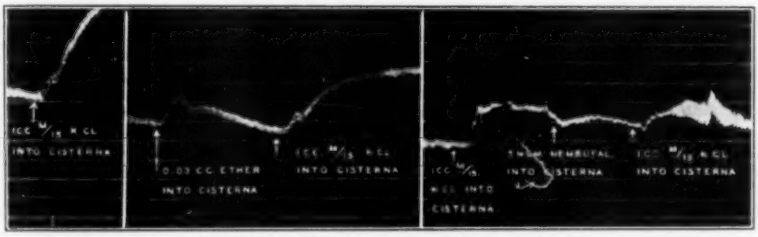
FIG. 2.—The marked pressor effect produced by potassium chlorid (*A*) was not obtained with sodium chlorid (*B*). Since the latter solution was five times as concentrated the records indicate that the pressor response could not have been due to increase in osmotic pressure.

The intravenous injection of equivalent amounts of potassium chlorid had no effect on blood pressure and produced no obvious changes in the general state or in the breathing of the animals. It is, however, of interest to note that Harrison, Friedman and Resnik[3] observed respiratory stimulation following the intravenous administration of much larger amounts of potassium chlorid than were employed in our intracisternal injections. The same authors also observed an increase in the blood pressure in many of their experiments.

To eliminate the possibility that the pressor responses were dependent on the anesthetic employed, a few observations were made on dogs anesthetized with ether. Injections of potassium chlorid produced in them also a well-marked rise in blood pressure.

The pressor effect was sometimes diminished but was not abolished by the previous intracisternal injection of small amounts of ether or of sodium pentobarbital (Fig. 3). The anesthetic did not augment the pressor response. It, therefore, seems unlikely that the effects observed can be ascribed to the narcotics used. Quite possibly the anesthetics, which themselves lower blood pressure when given intracisternally, may tend to make the animal less responsive to the potassium chloride.

It has seemed desirable to determine, if possible, the location of the area through which the potassium chloride exerts its effect. The existence of a "vasomotor center" in the floor of the fourth ventricle has long been assumed, but its exact location is unknown.[4,5,6] Furthermore, the recent demonstrations of various vegetative centers in the hypothalamus[7,8,9] have suggested the possibility that the vasomotor effects of medullary lesions might be the result of injury to projection pathways from the hypothalamus rather than to a specific nuclear "center" in the medulla.



A *B* *C*

FIG. 3.—Following the injection of ether the pressor response (*B*) to potassium chloride was somewhat less than before (*A*). The record (*C*) is from another dog and shows that nembutal diminishes slightly the pressor response to potassium chloride.

In each of 4 dogs anesthetized with sodium barbital, the following experiment was performed. The medulla and cerebellum were exposed by wide removal of the occipital bone and arch of the atlas, and opening the dura. The arachnoid over the outlet of the fourth ventricle was incised. An opening was made in the bone and dura over the left occipital lobe sufficiently large to allow anterior retraction of the occipital lobe, exposing the tentorium. A small ureteral catheter connected with a tuberculin syringe was inserted into the fourth ventricle, after careful removal of any free cerebrospinal fluid with a small pledget of cotton. Through the catheter 0.1 cc. of a solution of potassium chloride (100 to 1000 millimolar) was injected. A prompt rise in blood pressure occurred in all experiments (Fig. 4*A*). Equal amounts of the solution were then placed upon the dorsal surface of the medulla (below the fourth ventricle) and subsequently upon the upper cervical cord. In no

instance was any effect upon blood pressure demonstrated following these procedures.

The occipital lobe was then elevated from the tentorium and the upper brain stem rapidly severed at the level (intercollicular) of the tentorium. Hemorrhage was controlled by a large moist cotton pack. As soon as the blood pressure reached a constant level (usually 15 to 25 mm. below the previous level), the injection into the fourth ventricle was repeated. In all experiments, a prompt rise in blood pressure occurred. This rise was similar in degree to that occurring previous to the section of the brain stem in 2 experiments (Fig. 4*B*) and was slightly less than that previously observed in the other instances. In 2 experiments, the medulla was then sectioned below the fourth ventricle and the injection immediately repeated. Pressor responses did not occur. Necropsy revealed

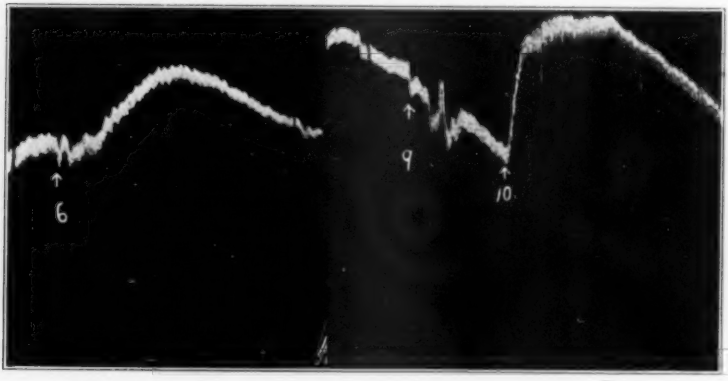


FIG. 4.—Section of the brain stem at the level of the tentorium (9) did not abolish the pressor response to potassium chlorid. (See text.)

complete intercollicular section in 3 of the 4 experiments. In the remaining one a small strand of the superior, lateral portion of the cerebral peduncle remained intact.

These experiments show that the site of action of the injected solution was between the inferior colliculus and the outlet of the fourth ventricle, and that the effect was mediated through pathways extending down the spinal cord rather than through the cranial autonomic efferent channels. On account of the rapidity of occurrence of the effect and the small volume of solution injected, it seems probable that this area lies close to the surface in the floor of the fourth ventricle.

Further studies concerning the more exact localization of the mechanism are in progress.

Calcium Salts. In view of the physiological antagonism[10] between potassium and calcium, it seemed desirable to investigate the

effects of intracisternal injections of calcium salts. Table 2 shows the results of such injections. The calcium salts injected were the chlorid, lactate and gluconate. These salts usually caused a slight decline in blood pressure, but marked diminution was not observed and in some instances no decrease occurred. A significant rise in blood pressure was not produced by calcium salts in any of the experiments.

TABLE 2.—THE EFFECT OF THE INTRACISTERNAL ADMINISTRATION OF CALCIUM SALTS IN THE ARTERIAL BLOOD PRESSURE OF DOGS.

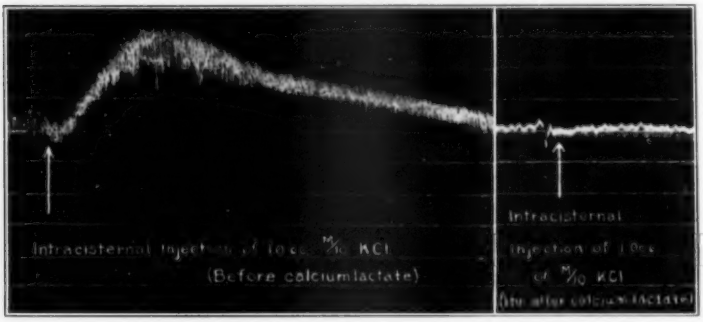
Date, 1934 to 1935.	Weight of dog, kg.	Calcium salt employed.*	Concentration of injected solution, millimols per liter.	Change in blood pressure, mm.Hg.
Dec. 7	14.6	Chlorid	50	− 5
		Chlorid	50	−10
20	10.3	Chlorid	100	−30
22	12.2	Chlorid	50	+ 5
28	6.0	Chlorid	5	−20
Jan. 5	10.5	Chlorid	5	− 5
Feb. 15	12.0	Chlorid	100	−20
		Lactate	(Suspension)	−10
21	10.2	Lactate	118	−10
23	11.3	Gluconate	100	−22
25	8.7	Lactate	50	0
26	8.0	Chlorid	50	− 5
		Lactate	50	− 8
		Gluconate	50	−15
27	8.1	Gluconate	50	−20
		Lactate	100	0
		Gluconate	50	−28
		Lactate	50	−10
28	12.1	Lactate	50	+ 5
		Gluconate	100	0
		Lactate	50	−15
Mar. 1	10.2	Gluconate	50	− 5
		Lactate	50	+ 5
		Gluconate	50	+10

* The amount of solution injected was 1 cc. in each instance.

In contrast to their relatively slight effects on blood pressure, calcium salts were found to have a striking inhibitory action on the pressor effect of subsequently injected potassium chlorid. Doses of the latter which regularly caused marked rise in blood pressure were entirely without effect when administered after calcium salts (Fig. 5). Even so small a dose as 1 cc. of two-hundredth molar calcium chlorid occasionally prevented the rise in blood pressure which otherwise would have followed injection of a much more concentrated solution of potassium chlorid (Fig. 6).

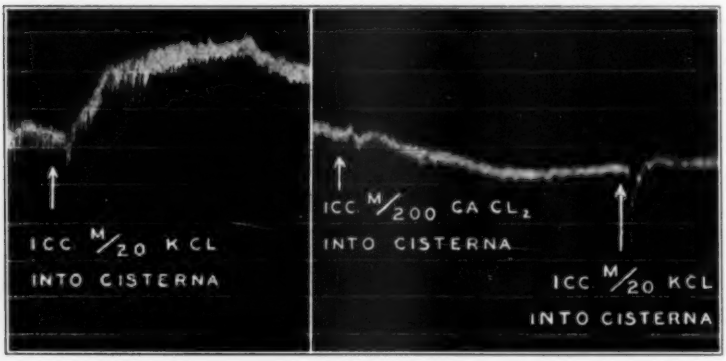
The duration of this inhibitory action of calcium salts varied in different dogs. A comparison (Table 3) of the three different salts seemed to indicate that when they were injected in equimolar amounts the gluconate had the most prolonged effect and the chlorid the least, the lactate being intermediate. A point which seemed of especial interest, and which is illustrated in Table 3, was

the lack of parallelism between the height of the spinal fluid calcium and the effectiveness of the calcium salt in preventing the rise of blood pressure produced by potassium injections. Thus, in several instances the effect of calcium salts in making the animal insensitive to potassium chlorid persisted after the calcium content of the cerebrospinal fluid had returned to a normal level. In other observations the animal recovered sensitivity at a time when the cerebro-



A B

FIG. 5.—The pressor response to potassium chlorid (*A*) was abolished by calcium lactate (*B*.)



A B

FIG. 6.—The very dilute solution of calcium chlorid (*B*) which caused relatively slight decline in blood pressure abolished the pressor response to potassium chlorid (*A*.)

spinal fluid calcium was still considerably elevated. These observations suggested that the calcium content of the nerve tissue rather than that of the cerebrospinal fluid is of chief importance in the inhibitory effect produced by this ion.

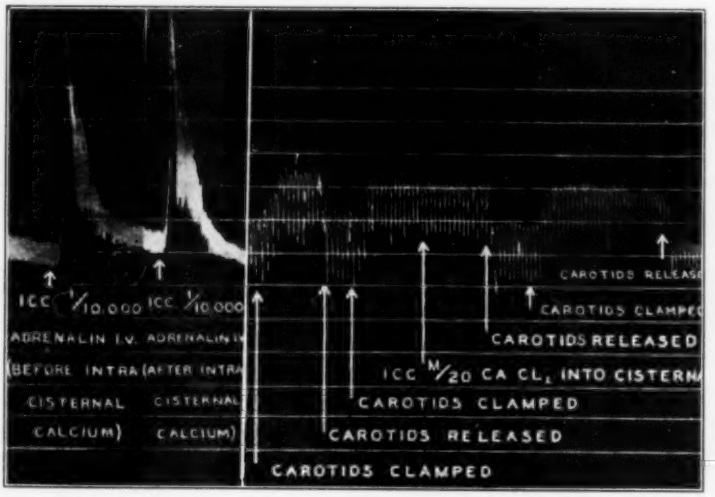
Observations were made in order to determine whether the intracisternal administration of calcium salts would have a general effect in abolishing or in diminishing pressor reactions which were

TABLE 3.—THE RELATION OF THE DURATION OF THE INHIBITORY EFFECT OF CALCIUM TO THE CALCIUM CONTENT OF THE CEREBROSPINAL FLUID.

Date, 1935.	Weight of dog, kg.	Calcium salt injected.*	Concentration of calcium salt, millimols per liter.	Duration of inhibitory effect, hours.	Spinal fluid calcium.		
					Before calcium injection.*	After calcium.	
						At end of period of inhibition.†	At time of recovery of sensitivity.
Feb. 15	12.0	Chlorid	100	2.6	3.2	11.9	9.5
		Lactate	250 (Suspension)	5.5	7.2	5.7	
21	10.2	Lactate	117	4.0	5.2	7.1	
23	11.3	Gluconate	100	4.0	5.1	9.0	4.3
25	8.7	Lactate	50	6.0	4.8	6.4	6.4
		Chlorid	50	3.1	9.0	5.1	5.3
26	8.0	Chlorid	50	2.0	4.2	8.3	6.1
		Lactate	50	3.0	5.4	9.8	7.3
		Gluconate	50	5.0+	5.7	7.0	
27	8.1	Gluconate	50	2.5	5.1	11.0	8.3
		Lactate	50	2.0	6.5	10.5	7.4
		Gluconate	50	1.1	6.4	52.9	8.8
		Lactate	50	0.5	5.7	51.4	5.2
28	12.1	Lactate	50	2.0	4.9	5.1	3.5
		Gluconate	50	3.0	5.4	5.2	4.8
		Lactate	50	2.0	4.7	8.9	3.8
Mar. 1	10.2	Gluconate	50	3.0	5.0	11.5	7.9
		Lactate	50	2.0	5.0	7.1	7.3

* The dose injected was 1 cc. in each instance.

† At the time when these samples were withdrawn the animals were still insensitive to potassium injections. The values in the next column are for samples taken when the animals had recovered sensitivity to potassium injections.



A *B*

FIG. 7.—The injection of calcium intracisternally did not change the response to adrenalin (Fig. 7*A*) or to clamping the carotids (Fig. 7*B*).

not due to central chemical stimuli. As is illustrated in Fig. 7*A*, the response to adrenalin was not altered by the administration of calcium into the cisterna. Similar negative results were obtained as regards the carotid sinus reflex (Fig. 7*B*). The degree of rise in blood pressure produced by clamping the carotid arteries was not altered by calcium injections. It appears, therefore, that the inhibitory action of calcium on pressor agents does not include those which increase the blood pressure through reflex mechanisms or through action on the peripheral vessels.

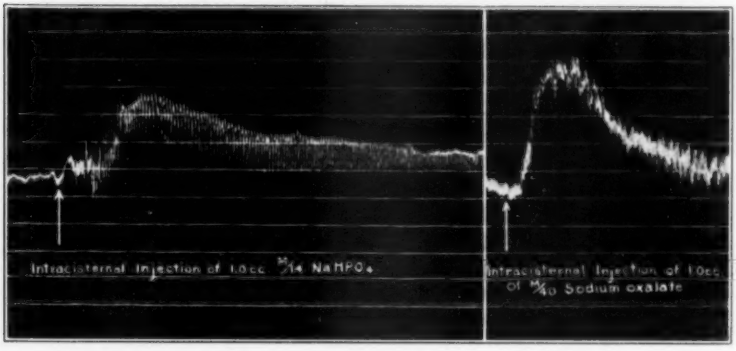


FIG. 8.—Disodium phosphate and sodium oxalate caused pronounced increase in blood pressure.

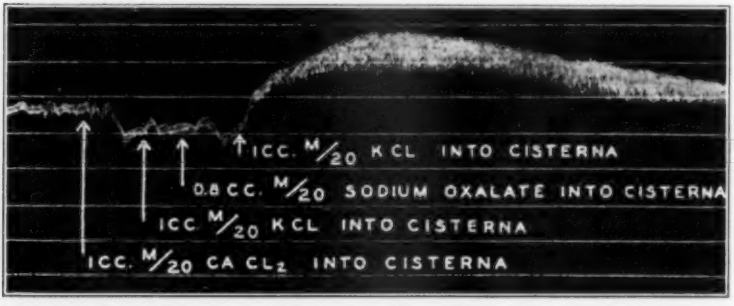


FIG. 9.—Following the injection of calcium chlorid no pressor response was obtained from potassium chlorid. This inhibitory effect of calcium chlorid was removed by the injection of sodium oxalate, the animal now reacting with a marked rise in blood pressure when potassium chlorid was again injected.

The Effect of Anions. No significant effects on blood pressure were noticed after the injection of 1 cc. of the sodium salts of chlorid, sulphate and nitrate in concentrations up to 200 millimols per liter. With larger doses slight increases in blood pressure—apparently due to osmotic effects—were observed. Pronounced rise in blood pressure occurred following the intracisternal administration of di-sodium phosphate, sodium oxalate and sodium citrate

(Fig. 8). These effects could be prevented by the previous administration of calcium salts. Furthermore, administration of these anions abolished the inhibitory effect of calcium salts on the pressor response to potassium chlorid (Fig. 9).

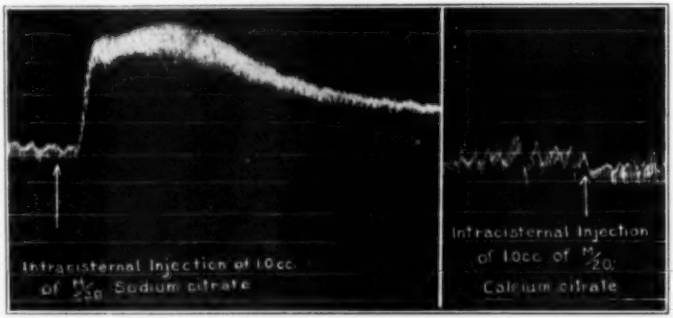


FIG. 10.—The negative result from calcium citrate appears to indicate that the positive response to sodium citrate was due to the calcium binding property of the citrate ion.

The injection of sodium phosphate and sodium oxalate, as expected, was found to cause a marked decrease in the total soluble spinal fluid calcium content. However, the injection of sodium citrate caused a significant decrease in the spinal fluid calcium content in only 1 of 5 observations (Table 4). It is known that citrate

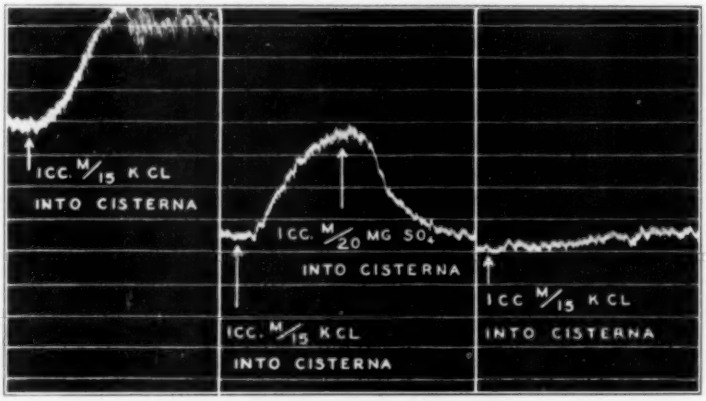


FIG. 11.—When given at the height of a pressor effect produced by potassium chlorid, magnesium sulphate was followed by a decline in blood pressure. A subsequent injection of potassium chlorid was now ineffective.

binds calcium as an un-ionized complex. This fact coupled with the observation that the injection of calcium citrate had no effect (Fig. 10) seems to indicate that the effect of calcium chlorid and lactate is independent of the total concentration and is related only

to the ionized calcium. Since there is evidence which suggests that the choroid plexus is relatively impermeable to calcium salts,[11,12] the rise in spinal fluid calcium, which occurred in certain instances,

1 CC. M/15 LEAD NITRATE INTRAVENOUSLY
15 MINUTES AFTER INTRAVENOUS LEAD
1 CC. M/15 LEAD NITRATE INTO CISTERNA (30 MINUTES AFTER LEAD INTRAVENOUSLY)
15 MINUTES AFTER LEAD INTRACISTERNALLY
30 MINUTES AFTER LEAD INTRACISTERNALLY

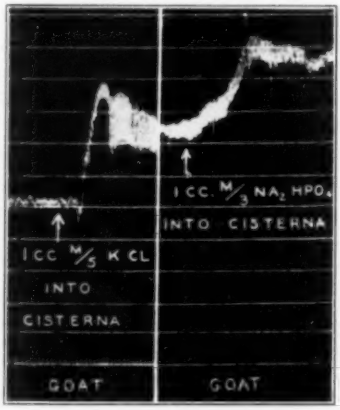
FIG. 12.—In the dose used lead had no effect when administered intravenously. Following intracisternal injection there was an immediate but temporary rise in blood pressure. A few minutes later a prolonged pressor response developed which endured for 30 minutes.

following the injection of citrate can best be explained by the assumption that calcium diffused out of the tissues of the nervous system into the cerebrospinal fluid.

TABLE 4.—THE EFFECT OF SODIUM CITRATE ON SPINAL FLUID CALCIUM.

Date, 1935.	Before.	After.	Amount of sodium citrate.
Feb. 5 . . .	3.8	5.0	1 cc. M/20 sodium citrate.
	4.6	7.1	20 min. after 1 cc. sodium citrate.
6 . . .	5.8	5.4	About 2 min. after 1 cc. M/20 sodium citrate.
		5.7	About 10 min. after 1 cc. M/30 sodium citrate.
Apr. 15 . . .	4.7	3.7	1 cc. M/50 sodium citrate.
	4.0	4.2	1 cc. M/50 sodium citrate.

Magnesium Salts. Only a few observations have been made using the chlorid and the sulphate ions. Insofar as the experiments go, they indicate that these salts have an action similar to, but less pronounced than that of calcium salts (Fig. 11). Doses which in themselves had little or no effect on blood pressure produced a pronounced inhibition of the pressor effect of potassium salts. The duration of this inhibitory action appeared to be shorter than when calcium salts were used. With large doses of magnesium chlorid or sulphate, respiratory paralysis and terminal rise in blood pressure, apparently due to asphyxia, occurred. When magnesium salts were administered at the height of the pressor effect produced by potassium, the blood pressure fell rapidly to a normal level in some observations but not in others.



A *B*

FIG. 13.—The two curves represent two different goats. Potassium chlorid (*A*) and disodium phosphate (*B*) caused well-marked rise in blood pressure.

Lead. In view of the clinical evidence[13] which points toward a relationship between plumbism and increased blood pressure, observations were made concerning the effect of lead nitrate when administered into the cisterna. Single large doses of lead nitrate produced a marked and sustained rise in arterial pressure. When smaller amounts were used a decline in blood pressure from the first injection was obtained, followed by an increase after subsequent doses. The pressor effects of small doses are slower in onset

and more prolonged than those produced by potassium chlorid. Doses of lead nitrate which are without effect when injected intravenously may cause a marked rise in blood pressure when given into the cisterna. These observations are illustrated in Fig. 12.

B. Observations on Goats. In order to determine whether the effects observed in dogs were due to some species peculiarity, it seemed desirable to make observations on other animals. Goats were chosen because they were of a convenient size and further because they represented a species of mammal far removed from the dog.

Goats proved less satisfactory than dogs as experimental animals because they were less readily anesthetized with sodium pentobarbital, and doses sufficient to keep them quiet were likely to be fatal. In two observations not complicated by this difficulty, the qualitative responses were similar to those found in dogs. Fig. 13 illustrates the effects of potassium chlorid and of sodium phosphate.

Discussion. The foregoing results, which are similar in a general way to those obtained by Hastings[18] in a study of the mechanism of tetany, indicate that the arterial blood pressure may be markedly influenced by changes in the electrolyte pattern of the cerebrospinal fluid, and that the effects may be exerted through a nerve mechanism situated in or near the floor of the fourth ventricle.

The most pronounced changes in blood pressure have been obtained by alterations in the amounts of potassium or calcium. It is well known[14,15] that these cations have marked influence on cell permeability, but whether any relationship exists between this action and their effects on blood pressure is uncertain.

Kylin[16] suggested that the increased peripheral resistance of patients with hypertension is the result of disturbance in the sympathetic nervous system secondary to changes in the K/Ca ratio. Weinstein and Weiss,[17] who reviewed the literature on this subject and reported a large series of cases, concluded that the available evidence does not favor this assumption. Calculations from our experiments indicate that the potassium content of the spinal fluid would have to increase by 50 to 100% to produce a marked elevation of blood pressure. (Of course, there is the possibility that man is more sensitive than the anesthetized dog to changes in the concentration of potassium.) More must be known about the amount and state of potassium in nerve cells before a justifiable claim can be made concerning a possible rôle of potassium salts in the production of hypertension.

Of the several anions which cause an increase in blood pressure when injected into the cisterna, phosphate is the only one which is known to accumulate in the body in pathologic states. The recent work of Hastings[18] and of McLean and Leiter[19] have supported the idea that the muscular twitchings of uremia are dependent on a diminution in the amount of ionized calcium in the body fluids, as the result of phosphate retention. Possibly the additional

increase in blood pressure which often occurs in the uremic state is related to the same mechanism, but further evidence is needed before this point can be regarded as established.

The frequency of hypertension in persons exposed to lead has been emphasized by Pal[20] and by Riegel.[21] The experiments of Tscherkess,[22] who showed that lead caused contraction in isolated vessels, pointed toward a peripheral action of this metal. However, our experiments showed that doses which are ineffective intravenously may cause a pronounced elevation when given intracisternally. It seems likely, therefore, that lead hypertension may be due to the deposition of the metal in the nervous system. In favor of this point of view is the fact that lead encephalopathy is accompanied by increase in blood pressure, as Fishberg[13] has emphasized.

Summary. The intracisternal administration of potassium chlorid caused a marked rise in the blood pressure of dogs. Similar doses of sodium chlorid were without effect. Calcium salts produced only slight decline in blood pressure but had a marked and prolonged effect in preventing a rise in blood pressure from subsequent injections of potassium chlorid. Salts such as oxalate, phosphate and citrate, which diminish the ionization of calcium, had marked pressor effects. Salts of magnesium had an action similar to, but less marked than that of calcium salts. Lead caused a delayed but prolonged rise in blood pressure. All of these actions were observed following the intracisternal injection of doses which were ineffective when administered intravenously.

The site of action of these electrolytes appeared to lie in or near the floor of the fourth ventricle. Effects persisted after section of the brain stem above this level, were not obtained after section below, and were elicited by the application of as little as 0.1 cc. directly to this area.

Goats reacted similarly to dogs but seemed to be less sensitive to the various electrolytes.

Since the inhibitory effect of calcium on subsequently injected potassium did not parallel the concentration of calcium in the cerebrospinal fluid, it is believed that the diffusion of calcium into the nerve cells was responsible for its effects.

Since the injection of calcium citrate was ineffective and since the administration of sodium citrate, although sometimes causing an increase in the total calcium content of the spinal fluid, had an effect similar to that from oxalate and phosphate, it is concluded that only the ionized calcium is of importance in inhibiting the blood pressure response to pressor electrolytes.

All of these electrolytes, if given in large doses, produced death by respiratory paralysis. Marked initial stimulation of breathing was produced by potassium, phosphate, oxalate and citrate, but not by calcium and magnesium. The former salts also caused general restlessness and muscular twitchings. These effects were relieved by ionized calcium salts.

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BLOOD TRANSFUSION IN TYPHOID FEVER.

By Pedro T. Lantin, M.D., D.T.M.

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF THE PHILIPPINES,

AND

Fortunato S. Guerrero, M.D.,

FORMERLY RESIDENT SURGEON, PHILIPPINE GENERAL HOSPITAL,

MANILA, P. I.

In our first paper[3] on this subject we reported favorable results in 10 severe cases of typhoid fever treated with blood transfusion. Since that time, we have continued using blood transfusion as a

treatment of severe cases of typhoid fever showing symptoms of marked toxemia. Our present series included only unmistakable cases of typhoid fever verified by blood culture. Our controls were also positive in blood culture and they were given the regular symptomatic treatment only. Our transfused cases and controls were taken from the same group of patients, in such a way that each group represented as far as possible the same severity of the disease in the same period of time, matched individually as closely as possible. Alternative controls could not be made because we could not obtain serial cases of the same severity in the same period of the disease and available at the same time; but we made it a point to select our patients from the severe cases as indicated not only by the clinical symptoms, but also by positive blood culture in every instance. In another report[4] the writers have had occasion to present the prognostic value of blood cultures in this disease and it is because of this fact that we have persisted in making blood culture tests in all of our cases.

Procedure. We remove 150 cc. of blood from the patient and immediately replace them by direct transfusion of 200 cc. of blood from a donor. We purposely started the blood exchange with small amounts, so that we could repeat the treatment as frequently as warranted by the circumstances. If no favorable reactions were observed, or if marked toxemia returned, we repeated the blood exchange *the day following or as often and as many times as required by the severity of the cases* after an interval of 2 to 4 days. Sometimes, we gave as many as 7 transfusions.

In cases, however, where there was intestinal hemorrhage, we did not remove blood from the patient but proceeded at once to transfuse 200 cc. of blood from the donor. Intestinal hemorrhage in itself is already a natural method of exsanguination, so we believed that no further withdrawal of blood from the patient would be necessary or advisable.

Observations. So far, we have treated 41 severe cases of typhoid fever with blood transfusion and 34 cases without. We have succeeded in reducing the fatality from 47.05% in the cases of our control (without blood transfusion) to 24.39% in our transfused cases (Table 1).

TABLE 1.—FATALITY OF TYPHOID FEVER WITH BLOOD TRANSFUSION (1933–1934).

	Recovered.	Died.	Total.	Fatality rate, per cent.
Transfused	31	10	41	24.39
Non-transfused (control)	18	16	34	47.05

Discussion. The rationale of our method of treatment is based on the principle of detoxication brought about by the withdrawal of blood from the patient and its immediate replacement with new blood from a donor. One can easily realize how the removal of the blood of a typhoid patient, loaded with the typhoid toxins and the introduction of new fresh blood from a donor, would bring into the system new protective elements against the disease. We agree with Tremelieres and Tzanck that "blood transfusion is capable of increasing and stimulating the organic defenses already insufficient or

decreased.[5] . . ." Furthermore, it is well known that blood transfusion has always an excellent antihemorrhagic effect.

In some old treatises on internal medicine, we read that many clinicians used to remove blood from their typhoid patients without however giving them a blood transfusion. For instance, Grisolle[2] withdrew from 12 to 16 ounces of blood which, at times, he even repeated twice consecutively; Chirac,[2] 4 to 5 cups every 13 hours until the pulse improved; Forget,[2] 28 ounces; Bouillaud,[2] 3½ pounds, and Louis,[2] 12 ounces to be repeated in severe cases. However, this method of typhoid treatment was later discontinued and fell into disuse for many years. Even in our modern medical literature, we find reports of some clinicians employing simple blood transfusion without partial exsanguination in typhoid fever, particularly in cases with intestinal hemorrhages, but apparently in no case was the treatment followed up sufficiently to make of it one of the more classical therapies of our present days.

For our part, we use partial exsanguination followed at once by blood transfusion as a general treatment in our severe cases of typhoid fever. We believe that this procedure brings about a more rapid detoxication and an early neutralization of the poisons in the system, an immediate introduction of protective elements and the stimulation of the defenses of the body.

The idea of detoxication by partial exsanguination is borne out by clinical observations in typhoid patients with moderate or even severe hemorrhages, after which, convalescence begins in many cases.

The beneficial results of this kind of treatment are readily seen in Table 1. The fatality was actually reduced from 47.05% in non-transfused cases to 24.39% in those that were transfused. As in our previous observations,[4] here again we were able to test the important significance of continued positive blood culture in the appreciation of the ultimate outcome of the case.

After blood transfusion, we have generally observed a decrease in temperature, usually from 2 to 4 days accompanied by a decided improvement of the pulse which becomes stronger and more regular, and a gradual subsidence of other toxic symptoms with a general improved feeling on the part of the patient.

Some cases, however, may develop chills or chilly sensations a quarter or half an hour after the transfusion, lasting for several minutes and followed usually by a momentary rise in temperature which becomes normal or subnormal after a short time, in some cases accompanied by sweating. This temperature soon rises again to about the same level as before the injection but will gradually subside afterwards in favorable cases.

In about half of our series of 41 cases, we have repeated the transfusion of blood as circumstances demanded, as follows:

1 blood transfusion to 22 cases, 2 in 10 cases, 3 in 6 cases, 4 in 1 case, 5 in 1 case, 7 in 1 case.

Treatment by immuno-transfusion is based on the theory that blood which has acquired immunization in typhoid either by actually having had the disease or by vaccinations will be more effective in the treatment of this particular disease. This was true with the observations of Becart,[1] Tremelieres and Tzanck[5] who found good results in the treatment of typhoid fever with immuno-transfusion. But on the other hand, Weil, Rouillard, Netter, Andibert, Tixier and Seze[5] have observed beneficial results with the use of non-immunized blood. We have also begun observations along these lines but until now, we do not feel justified to report them. We have obtained some promising results, but the number of our cases is still too small to warrant definite conclusion.

Summary. This material is presented as a preliminary report; for it is realized that the observations are rather limited and the number of cases (41) included in our series is comparatively small.

Purposely, the author selected only these cases of typhoid fever that were regarded as severe, verified by positive blood culture and with marked toxemic manifestations.

The study was carried as far as possible under similar conditions for the treated and the control cases.

Partial exsanguination has always been practiced immediately preceding blood transfusion, except in those cases where intestinal hemorrhages had occurred.

The fatality percentage was reduced from 47.05% in the control cases to 24.39% in the treated cases.

Conclusion. In spite of the limited number of cases and in view of the promising results obtained, it is thought that this method is of sufficient value that it should be given a fair trial by others in the near future.

The writers desire to express thanks and appreciation to President Jorge Bocobo of the University of the Philippines, and to Dean Fernando Calderon of the College of Medicine, for their generous grants which made these observations possible.

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3. Lantin, P. T., and Guerrero, F.: Preliminary Report on the Treatment of Typhoid Fever by Partial Exsanguination and Blood Transfusion. J. Philippine Islands Med. Assn., **13**, 411, 1933.

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BOOK REVIEWS AND NOTICES.

FOR AND AGAINST DOCTORS. An Anthology Compiled by ROBERT HUTCHISON and G. M. WAUCHOPE. Pp. 168; illustrated. Baltimore: William Wood & Co., 1935. Price, $2.00.

THIS urbane little anthology pretends to do no more than scratch the surface of the vast corpus of opiniative literature on the virtues and vices of the practitioners of the world's second oldest profession. The material, most of which appeared originally in the *London Hospital Gazette*, is arranged in chronological order, beginning with proverbs of indefinable antiquity and concluding with such irrepressible, if sadly fading, moderns as G. B. S., G. K. Chesterton and Dean Inge, no one of these being very felicitously represented. The dicta come from many lands and many hands, and represent for the most part lay opinion. This ranges widely, as is to be expected, from the grossest abuse to the most unqualified endorsement. The wittiest expressions, as often the most profound, are to be sought in the former category, in accordance with the well-known frailty of human nature. But it is not easy to forget Stephen Paget's words (from the *Confessio Medici*) which conclude this anthology—"If a doctor's life may not be a divine vocation, then no life is a vocation, and nothing is divine."

It is much to be hoped that a more comprehensive collection of similar excerpts may someday be made, and that it may include more of what the doctors have had to say about themselves. It should not include the trivial, however illustrious the oracle, when the literature of all lands is so rich in original and pungent observations on the subject. Meanwhile, this prelude to the potential grand fugue ought to be in the library of every doctor with a sense of humor and a pride in his profession. W. McD., 2D.

DIE LIQUORDIAGNOSTIK IN KLINIK UND PRAXIS. By DR. HANS HEMME, Privatdozent für Neurologie, Chefarzt der neurologischen Abteilung des allgemeinen Krankenhauses Barmbeck in Hamburg. Pp. 205; 96 illustrations. München: J. F. Lehmanns, 1935. Price, Mk. 7.

A CONCISE treatise on the laboratory examination of the cerebrospinal fluid. There are introductory chapters on anatomy and physiology; then follow a description of the technique of the usual tests, and a clear exposition of normal findings. The latter half outlines the characteristics of the cerebrospinal fluid in the chief neurological and neurosurgical disorders. Pathologists, internists, and neurologists will value the book for the accessibility of its material, and for the clear description of the procedures advocated. W. J.

LES PARATHYROIDES. First Fascicle, Volume 2 of Traité d'Endocrinologie. By C. I. PARHON, Professeur à l'Université de Jassy, and M. GOLDSTEIN, Docent à l'Universite de Bucarest. Pp. 524; illustrated. Jassy: H. Goldner, 1935. Fr. francs, 40.

IN this first fascicle of Volume 2 of this treatise, the first that has reached us, the normal and pathological anatomy of the parathyroids, the human and comparative symptomatology of parathyroid disease, their relation to certain disorders of the bones, the skin and the nervous system and to

other endocrine disorders and parathyroid therapy are presented in considerable detail. In the very frequent references to the works of other writers, the volume resembles a monograph more than a textbook; but unfortunately for those wishing to use it as a reference book, the bibliography has been reserved for the second fascicle, which will be on the thymus. One misses an index also, as is customary in books in French; with the method of composition used in this book, an extensive index would have been especially valuable. E. K.

THE CEREBROSPINAL FLUID AND ITS RELATION TO THE BLOOD. A Physiological and Clinical Study. By SOLOMON KATZENELBOGEN, M.D., Associate in Psychiatry, in charge of The Laboratory of Internal Medicine, The Henry Phipps Psychiatric Clinic, The Johns Hopkins Medical School, etc. Pp. 468; 48 tables and 20 charts. Baltimore: The Johns Hopkins Press, 1935. Price, $5.00.

THIS reference book is divided into two parts. The first three chapters deal with the origin of the cerebrospinal fluid, its mode of formation, and circulation. The remainder of the volume is devoted to the chemical constitution of the fluid compared to that of blood.

In a reference work the reader hopes to find each chapter introduced by a statement of the problem followed in turn by a marshalling of data, critical comments and conclusions, and a summary; at the end of the book a complete bibliography and a workable index. Such is the author's plan. Of the components mentioned, only the first leaves something to be desired. Particularly commendable is the scrupulous separation of data from the author's comments. The result is a scholarly and prudent treatise, worthy of a place on the shelf of every researcher in the subject. For the rare gift of an incisive style that points the challenge of the chosen field, the reader of this volume seeks in vain. G. McC.

POLLEN GRAINS. Their Structure, Identification and Significance in Science and Medicine. By R. P. WODEHOUSE, PH.D., Scientific Director of the Hayfever Laboratory, The Arlington Chemical Company, Yonkers, New York. Pp. 574; 123 illustrations and 14 plates. New York: McGraw-Hill Book Company, Inc., 1935. Price, $6.00.

FAR and away the finest text available on the subject of pollen grains from the medical point of view. In Part I, after an interesting historical review, the author discusses methods of collecting pollen in large amounts, preparation of pollen for microscopic examination, atmospheric pollen, hayfever, pollen-grain characteristics. There is a chapter by Professor Gunnar Erdtman of Stockholm on pollen statistics, especially as applied to geologic research. Part II is a key and classification of pollen grains for purposes of identification. The numerous excellent illustrations are for the most part drawings by the authors. All physicians interested in the rôle of pollen grains in the causation of human disease owe Mr. Wodehouse a great debt of gratitude. R. K.

KLINIK UND THERAPIE DER ALLERGISCHEN KRANKHEITEN. By DR. ERICH URBACH, Privatdozent für Dermatologie an der Universtät Wien. 1. Assistant der Universitätsklinik für Geschlechts- und Hautkrankheiten in Wien (Vorstand PROF. DR. W. KERL). Pp. 781; 302 illustrations (26 in colors) and 24 tables. Wien: Wilhelm Maudrich, 1935. Price, Rm. 30.

THE first part of the book is devoted to general and theoretical considerations of the subject, including a detailed discussion of types of hyper- and hyposensitivity, researches in experimental anaphylaxis, the pathogenesis

of allergy, allergens, antibodies, the factors predisposing to allergy, the tissue manifestations of allergy, technique of testing for allergy, preparation of allergens, principles of treatment of allergy. These subjects are well covered and the existing literature is skillfully evaluated.

Part II deals with the special manifestations of allergy, their diagnosis and treatment. Allergy of the respiratory tract (asthma, hay fever, allergic rhinitis) is handled a bit sketchily, although adequately from the standpoint of the general practitioner. Particularly well done are the allergic conditions of the skin, a field in which the author, primarily a dermatologist, has made numerous and valuable contributions. There is appended a very useful table of concentrations of materials to be used in patch testing. Allergists and dermatologists alike will find this volume helpful and worthwhile. R. K.

GLANDULAR PHYSIOLOGY AND THERAPY. A Symposium Prepared under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 528; 7 charts; 8 illustrations. Chicago: American Medical Association, 1935. Price, $2.50.

THIS physically well made book is the best work of its kind known to the Reviewer. There are 31 chapters by 26 authors, covering the points of major interest in modern endocrine physiology and therapy. With the exceptions of Aschheim and Zondek, all contributors are American or Canadian authors who are recognized authorities on the subject about which they write. Each chapter has a separate bibliography. There is an index. All of the articles have previously appeared in the *Journal of the American Medical Association.* F. D.

CARDIAC OUTPUT AND ARTERIAL HYPERTENSION. By SIDNEY A. GLADSTONE, M.D. Pp. 56; illustrated. New York: By the Author, 1935. Price, $1.00.

THIS 56-page monograph is little more than an elaboration of several papers published recently by the same author. The Grollman Cardiac Output Method has been reinvestigated, is criticized, and a modification developed. This new technique has been employed to estimate cardiac output in a few cases of hypertension. A long theoretical discussion of the causation of hypertension follows. I. S., JR.

DIE THEORETISCHEN GRUNDLAGEN UND MÖGLICHKEITEN DER RÖNTGENDIAGNOSTISCHEN WEICHTEILUNTERSUCHUNG. (Forty-eighth supplementary volume of Fortschritte auf dem Gebiete der Röntgenstrahlen.) By DR. ADOLF ZUPPINGER. Pp. 99; 46 illustrations. Leipzig: Georg Thieme, 1935. Price: Paper, Rm. 16; Bound, Rm. 18.

THIS excellent monograph deals with physical factors that radiologists have empirically come to regard as necessary for high quality films. The subject matter, though technical and replete with formulæ and physical measurements, is admirably presented. While the author does not outline the actual technique for the various Roentgen examinations, he does analyze the importance of the various factors, such as wave length, time of exposure, secondary irradiation, gamma value of films, filtration, screen illumination and the part they play in obtaining excellent roentgenograms. The book contains numerous illustrations and charts which enhance its value. P. H.

INFANT NUTRITION. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAMS MCKIM MARRIOTT, B.S., M.D., Professor of Pediatrics, Washington University School of Medicine; Physician in Chief, St. Louis Children's Hospital, St. Louis. Pp. 431; 27 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1935. Price, $4.50.

THIS new edition of Dr. Marriott's book covers in an interesting and yet concise fashion the important aspects of the nutrition of children. A number of changes have been made in this edition, some of which add to its value and some do not appeal to this Reviewer at all. Important advances in our knowledge of the vitamins necessitated complete revision of the appropriate chapter and this has been well done. A new chapter on the relation of allergy to the feeding of children has been added. While perhaps too abbreviated for the man specializing in Pediatrics, it presents adequate information for the cursory reader. Slight revisions throughout the rest of the book have been necessary due to recent progress.

The Reviewer regrets that the publishers did not use the same paper and type as in the previous edition. Most of us read with artificial light and the paper and print of the first edition were kind to eyesight even though some charts were not as clear cut. The author has combined in a greatly condensed form information concerning anhydremia, acidosis and alkalosis occasioned by diarrhea and vomiting in the appropriate chapters on these subjects. True, many of the charts of the old edition were more appropriate to a monograph but the bulk of the chemical information offered a very clear exposition of those subjects to the student or practitioner. The Reviewer regards the new edition as too abbreviated in these matters. The chapters on Rickets, Scurvy and Tetany, while very well written, could be condensed for these topics befit the textbook on Pediatrics better though they should be mentioned in a volume of this type.

Marriott's Infant Nutrition is still the leading small book on this subject for the student. E. T., JR.

CLASSICAL CONTRIBUTIONS TO OBSTETRICS AND GYNECOLOGY. By HERBERT THOMS, M.D., Associate Professor of Obstetrics and Gynecology, Yale University. With a Foreword by HOWARD A. KELLY, Emeritus Professor of Gynecology, Johns Hopkins University. Pp. 265; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

ADVANCES in the fields of Obstetrics and Gynecology have been slower than in the sister branches of Medicine and Surgery. Furthermore, obstetricians as a group are not especially known for either their interest in research or for any outstanding interest in the history of their specialty. The present small volume on the history of Obstetrics and Gynecology makes an exception to the above statements. Thoms' contribution is a welcome one to this field of obstetrical textbooks; he has written a valuable book to those interested in obstetrics, and one within the price range of all.

For the first time, we have a small volume in which we can learn something regarding the life and times of past masters in obstetrics; and more especially can read in the original the classical contributions of these authors. Some 60 extracts of two or three pages each are preceded each by a paragraph about the author, while the 7 chapters have appropriate forewords.

Every chapter is interesting. The analysis of the material under appropriate headings such as pregnancy, labor, obstetrical operations, puerperal infection, pelvic deformities, and so forth, is of great assistance to the reader, and each contribution, frequently with a picture of its author, has its fascination for the student of obstetrical history.

The book is well composed: The type is large and clear; a useful bibliography and index are appended. The Reviewer's only complaint is that the author has perhaps been too brief. D. M.

ANATOMY OF THE RAT. By EUNICE CHACE GREENE. Vol. 27 of the Transactions of the American Philosophical Society, held at Philadelphia for Promoting Useful Knowledge. Pp. 370; 338 illustrations, partly in color. Philadelphia: The American Philosophical Society, 1935. Price, $5.00.

IN view of the extensive use of the albino rat for various laboratory purposes it is indeed surprising that there has hitherto not been any book on his normal anatomy more detailed than Hunt's Manual (1924) for students. The present work, somewhat comparable to the good human textbook of Anatomy, obviously therefore supplies a needed want, both for advanced students of Comparative Anatomy and for investigators using the albino rat. After preliminary dissections, thorough dissections were made of each system in at least 10 animals and drawings made by the author of the condition found in the majority. These numerous drawings add greatly to the value of the book. This work in conjunction with the data contained in H. H. Donaldson's "The Rat" (second edition, 1924) places knowledge of the anatomy of this animal far beyond that of any other lower animal and in some respects of man himself. E. K.

THE OBSTETRIC PELVIS. By HERBERT THOMS, M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, The School of Medicine, Yale University. Pp. 115; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1935. Price, $2.50.

THIS monograph presents in a collective manner the essence of the author's many published contributions to this subject, together with pertinent comments on those of others. He discusses normal and variant pelves in both their anatomical and clinical relations in a clear and lucid manner. Of specific interest are his observations on pelvimetry: the frequent findings of marked differences in the true or internal measurements as revealed by Roentgen ray, in contrast to what might have been expected from external pelvimetry substantiates his feeling that every primigravida should have roentgen pelvimetry. His technique for pelvic mensuration as well as for fetal cephalometry is given in detail. In an excellent chapter on the early determination of disproportion are his views as to the various factors concerned, and the value of roentgen pelvimetry. The funnel pelvis, the dolichopellic pelvis and the recent classification of the abnormal pelvis by Caldwell and Moloy are thoroughly considered. A valuable bibliography is appended.

This work should be of value both to the obstetrician and to his co-worker the roentgenologist. P. W.

BIBLIOGRAPHY ON BLOOD TRANSFUSION, VOLUME I. (International Bibliography on the Problems of Blood Transfusion and the Theory of Blood Groups, 1900–1933.) By DR. E. KOENIG. Pp. 226. Leningrad: Professor E. Hesse, 1935. Price, 12 p., 50 k.

THIS publication consists of a list of 4423 articles on blood transfusion and blood groups which have appeared in the world literature between 1900 and 1933. The finding of any article in the list is facilitated by classification into subtopics, a system of cross-indexing and an author index. The preface and section titles are written in Russian, German, English, French and Italian. Titles of articles in Russian or languages other than German, English, French or Italian are duplicated in German. Such a work as this is clearly of great value to anyone investigating the literature on blood transfusion. L. L.

NEW BOOKS.

Great Doctors of the Nineteenth Century. By Sir William Hale-White, K.B.E., M.D., LL.D. (Hon.), F.R.C.P., Consulting Physician to Guy's Hospital. Pp. 325. Baltimore: William Wood & Co., 1935. Price, $5.00.

American Martyrs to Science Through the Roentgen Rays. With a Short Glossary of the Scientific Terms used in the Text. By Percy Brown, M.D., F.A.C.P., F.A.C.R., Historian and Former President, American Roentgen Ray Society. Pp. 276; 55 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, $3.50.

Pediatric Nursing. By John Zahorsky, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine; Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc., assisted by Beryl E. Hamilton, R.N., Graduate of St. Luke's Hospital, St. Louis. Pp. 568; 144 illustrations and 7 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, $3.00.

Cardiac Output and Arterial Hypertension. By Sidney A. Gladstone, M.D. Pp. 56; illustrated. New York: By the Author, 1935. Price, $1.00. (Review p. 856.)

The Chemistry of Natural Products Related to Phenanthrene. By L. F. Fieser, Associate Professor of Chemistry, Harvard University. Pp. 358. New York: Reinhold Publishing Company, 1936. Price, $6.50.

Tuberculosis. (Vol 16 of Clio Medica Series). By Gerald B. Webb, Former President, National Tuberculosis Association; Lecturer on Medical History, University of Colorado; President, Colorado Foundation for Research in Tuberculosis. Pp. 205; 17 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, $2.00.

How to Feed Children in Nursery Schools. By Mary E. Sweeny and Dorothy Curts Buck, Physical Growth Staff, The Merrill-Palmer School. Pp. 84; illustrated. Detroit: The Merrill-Palmer School, 1936. Price, Gratis.

Die Werke des Hippokrates. Herausgegeben von Dr. Med. Richard Kapferer unter Mitwirkung von Prof. Dr. Georg Stricker, Würburg. Book 7 (Price, Rm. 7.50; Pp. 85): Die Natur (Konstitution) des Menschen; Die Nahrung; Die Säfte (The Nature (Constitution) of Man; The Nutriments; the Humors). Book 10 (Price, Rm. 5.25; Pp. 75): Die Krisen; Die Kritischen Tage; Prognostikon (The Crises; The Critical Days; Prognostics). Stuttgart: Hippokrates Verlag G.M.B.H., 1934 and 1936, respectively. (To be published in 25 parts costing *ca.* Rm. 100, card binding.)

Time of Ovulation in Women. A Study of the Fertile Period in the Menstrual Cycle. By Carl G. Hartman, Department of Embryology, Carnegie Institution of Washington, Johns Hopkins Medical School, Baltimore, etc. Pp. 226; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, $3.00.

Cancer Commission Committee Studies. The California Medical Association. (The results of a five-year correlated study by one hundred and fifty members of the medical profession). Pp. 123. San Francisco: J. W. Stacey, Inc., 1936. Price, 75c.

Medical Papers. Dedicated to Henry Asbury Christian. Physician and Teacher. From his Present and Past Associates and House Officers at the Peter Bent Brigham Hospital, Boston, Massachusetts. In Honor of his Sixtieth Birthday, February 17, 1936. Edited by Robert F. Monroe, Peter Bent Brigham Hospital. Pp. 1000; illustrated. Baltimore, The Waverly Press, 1936. (No price given.)

Medical History of Contraception. By NORMAN E. HIMES, PH.D. Medical Foreword by ROBERT LATOU DICKINSON, M.D., F.A.C.S. Pp. 521; 30 illustrations and 29 tables. Baltimore: The Williams & Wilkins Company, 1936. Price, $7.00.

Protoplasm. By WILLIAM SEIFRIZ, PH.D. (Johns Hopkins University), Professor of Botany, University of Pennsylvania, Philadelphia. Pp. 584; 179 illustrations. New York: McGraw-Hill Book Company, Inc., 1936. Price, $6.00.

Photoimmunization and Photovaccination. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 13. Cleveland: The S. P. Mount Printing Company, 1936. (No price given.)

The Surgical Clinics of North America, Volume 16, No. 1 (Chicago Number, February, 1936). Pp. 356; 78 illustrations. Philadelphia: W. B. Saunders Company, 1936. Price, Paper, $12; Cloth, $16 (per clinic year February–December, 1936).

Parenteral Therapy. A Ready Reference Manual of Extra-oral Medication for Physicians, Dentists, Pharmacists, Chemists, Biologists, Nurses, Medical Students and Veterinarians. By WALTON FOREST DUTTON, M.D., Formerly Medical Director, Polyclinic and Medico-Chirurgical Hospitals, Graduate School of Medicine, University of Pennsylvania, etc., and GEORGE BURT LAKE, M.D., Formerly Special Lecturer in Hygiene, Purdue University, etc. Pp. 376; 90 illustrations: Springfield, Ill.: Charles C Thomas, 1936. Price, $7.50.

NEW EDITIONS.

Basal Metabolism in Health and Disease. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College, New York; Physician-in-Chief to the New York Hospital. Pp. 494; 99 illustrations, 67 tables. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $5.00.

A Guide to Human Parasitology. For Medical Practitioners. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.); D.T.M. (LIVER.), Professor of Tropical Hygiene, Liverpool School of Tropical Medicine, The University of Liverpool, and formerly Professor of Parasitology; Director of the Sir Alfred Lewis Jones Laboratory, Freetown, Sierra Leone, West Africa, and T. SOUTHWELL, D.SC., PH.D., A.R.C. SC., F.Z.S., F.R.S.E., Walter Myers Lecturer in Parasitology, School of Tropical Medicine, The University, Liverpool, etc. Pp. 259; 122 illustrations, 2 colored plates. Second edition. Baltimore: William Wood & Co., 1935. Price, $4.00.

Lectures on Diseases of Children. By ROBERT HUTCHISON, M.D., LL.D., F.R.C.P., Consulting Physician to the London Hospital and to the Hospital for Sick Children, Great Ormond Street. Pp. 452; 106 illustrations. Seventh edition. Baltimore: William Wood & Co., 1936. Price, $6.75.

Roentgenographic Technique. A Manual for Physicians, Students and Technicians. By DARMON ARTELLE RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Baptist State, Missouri Pacific, and the Arkansas Children's Hospitals, Little Rock, Arkansas. Pp. 431; 183 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $5.50.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
FRANKLIN G. EBAUGH, M.D.,
PROFESSOR OF PSYCHIATRY IN THE UNIVERSITY OF COLORADO,
AND
GEORGE JOHNSON, M.D.,
PROFESSOR OF NEUROPSYCHIATRY, LELAND STANFORD UNIVERSITY.

THE POST-TRAUMATIC PERSONALITY DISORDERS.

THE great interest manifested during the past few years in the problems of mental disorders following head trauma continues unabated among psychiatrists and neurologists here and abroad. From both a scientific and a medico-legal standpoint these problems are assuming an ever increasing importance. Johnson[1] has briefly reviewed the contributions in this field up to 1934 in this journal. The present review will be confined to a consideration of the post-traumatic psychoneuroses and their organic counterpart, the so-called traumatic constitution or traumatic encephalopathy, disregarding the acute traumatic psychoses, post-traumatic mental deterioration, traumatic epilepsy, and the traumatic precipitation and aggravation of other psychiatric and neurologic disorders. These subjects, as well as the one under consideration here, have been discussed fully in a recent publication of Ebaugh and Benjamin.[2]

The differentiation of traumatic encephalopathy from functional disorders following trauma has not only therapeutic but also medico-legal significance, since many courts refuse or grant only reduced compensation to cases of post-traumatic psychoneurosis. The differential diagnosis can be extremely difficult, requiring minute neurologic and psychiatric examinations (Strauss and Savitsky[3] reviewed by Johnson).[1] The problem is further complicated by the frequent simultaneous occurrence of organic and functional post-traumatic manifestations in the same patient. It is therefore not surprising that considerable difference of opinion and perhaps some confusion still exist concerning these conditions. Several publications of the past year have contributed toward a clearer understanding of the issues involved.

Wechsler[4] presents a series of 100 cases of which 27 gave obvious objective evidence of brain injury, whereas the remaining 73 presented no gross signs of organic involvement but complained of subjective disturbances such as headache, dizziness, impairment of memory, fears, anxieties, vasomotor disturbances, tremors, impairment of vision. He places these post-traumatic syndromes in the following 4 classes: (1) Malingering, in which there is a conscious and purposeful feigning of illness in order to avoid responsibility or to derive gain (unalloyed malingering is extremely rare, being found only once in the author's series); malingering with hysteria was present in 2 cases; (2) post-traumatic hysteria, the most common post-traumatic sequela that is unaccompanied by gross organic involvement. Wechsler diagnosed this condition outright in 37 of his cases, in addition found hysteria with traumatic encephalopathy 17 times, and hysteria combined with malingering twice. He emphasizes that the diagnosis should be based on both negative and positive criteria, including under the former a history of either no or very brief unconsciousness, no clinical signs of brain injury, no evidence of fracture, and a negative encephalogram; and under the latter positive evidence of a true hysterical reaction precipitated by trauma in an individual with an underlying neurotic personality. The trauma sets in motion the same mental mechanisms as in any other hysteria and serves as a convenient solution of industrial, social, marital, familial or psychosexual conflicts; (3) concussion or traumatic encephalopathy, found in 11 cases alone, and in 17 cases in combination with hysteria. In every case there was a history of more or less prolonged unconsciousness; minute neurologic signs were found in only a few. Typical for these causes are the history of unconsciousness, the absence of psychogenic causal factors, the persistence and severity of the symptoms, and positive encephalographic findings. The author quotes Martland,[5] Foerster and Penfield,[6] Bielschowsky,[7] Rand and Courville[8] and Friedman[9] as having contributed greatly to the knowledge of the anatomic changes underlying this condition, such as minute hemorrhages, glial changes, cell and fiber degeneration, disturbed cerebrospinal dynamics, ventricular distortion, and brain atrophy; (4) traumatic neurosis, diagnosed in 5 cases. Wechsler calls attention to the fact that this term is frequently used synonymously with traumatic hysteria, but believes that one is here dealing with two distinct entities. Clinically this condition differs little from hysteria, but it is apparently not dependent on the unconscious use of the accident to solve difficulties that have nothing to do with the trauma. One is not dealing with a patient who has a neurotic personality to begin with, but rather with a previously well adjusted individual who, following a serious threat to life, without serious head injury, develops symptoms which are not amenable to suggestion or other forms of psychotherapy. There are no demonstrable cerebral changes, hysterical mechanisms cannot be elicited, and compensation does not play a predominant rôle.

Ebaugh and Benjamin[2] point out that the contributors to this field vary greatly in their use of terms, evaluation of symptoms, and estimation of the frequency and medico-legal disposition of the various conditions to be differentiated. After mentioning the contributions

of Brun,[10] Kardiner,[11] Kennedy,[12] Hall and Mackay,[13] Monakow,[14] Naegeli,[15] Riese,[16] Ritter,[17] Rosenstein,[18] Schaller and Somers,[19] Sperling,[20] Strauss and Savitsky,[3] and Wechsler,[4] they suggest the following classification of the post-traumatic minor personality disorders, which in many respects coincidents with that of Wechsler:

I. Traumatic encephalopathy (traumatic constitution): A, Simple type, with subjective complaints of headache, vertigo, irritability, fatigue, impairment of memory; B, with secondary psychogenic symptoms; C, with malingering.

II. Post-traumatic functional disorders: A, Post-traumatic hysteria (rarely other psychoneuroses): a true hysteria precipitated by trauma in an individual with an underlying neurotic personality; may be accompanied by malingering; B, compensation neurosis: a hysteria in which the wish for compensation plays a leading rôle in the unconscious production of symptoms; may be accompanied by malingering; C, traumatic neurosis or terror neurosis: a neurosis, usually hysteriform with pronounced anxiety features, in which the psychogenic mechanisms differ from those in ordinary hysteria.

III. Malingering.

In their discussion of traumatic encephalopathy the authors emphasize that no physician is justified today in denying the existence of organic factors in post-traumatic cases on the basis of a cursory neurologic examination and the impression that the patient is a "neurotic." Kennedy's[12] anamnesic and clinical criteria are presented (Johnson[1]); they are held to be of great value in giving a general orientation as to the probabilities in any case, but not to be conclusive evidence. The authors, in common with Strauss and Savitsky,[3a] stress the importance of a minute neurologic examination; minimal signs will be found in a great many although by no means all cases. Slight differences in reflexes on the right and left side, diminished vibratory sensation in both lower extremities, diminished corneal reflexes, and difficulty in lateral conjugate gaze are mentioned as but a few of the many findings reported. The authors' own experience confirms the opinion of Foerster,[21] Förster and Penfield,[6] Friedman,[9] and many others that encephalography is a highly valuable adjunct to clinical investigation in this field. They emphasize further the great importance of a detailed formal psychiatric examination, particularly of the sensorium. Special tests for apperception, retention and recall, memory, and organic fatigability are recommended. The Rorschach test is mentioned as being of great value in cases where the differential diagnosis between encephalopathy and the functional syndromes is particularly difficult, and reference is made to the work of Oberholzer[22] in this respect.

In their consideration of the functional post-traumatic disorders and malingering, the authors agree fully with Wechsler's[4] definition and delimitation of the latter term, and share his opinion that unalloyed malingering is rare. In discussing the psychoneurotic reactions, they point out that whereas *a priori* it might be expected that any type of neurosis could be precipitated by head injury, empirically almost all of these cases are hysterias, with or without anxiety, and regard this as due to the specific predisposition of the hysterical personality to use all possible situations as a means of escape into illness, as well as to the

abnormal suggestibility of the hysterical personality. They furthermore agree with Wechsler that the diagnosis should not be made merely through the exclusion of organic signs, but requires positive evidence of hysterical mechanisms. They base their differentiation of compensation neurosis from other post-traumatic hysterias not on the grounds of true etiology, which in both cases lies in conflicts which have no relation to the trauma, but rather on the practical grounds that in some patients the compensation motive plays a leading rôle in the production and persistence of symptoms, and that in these cases a lump sum settlement is the best and usually the only therapy. In opposition to Naegeli and others, they do not feel that the compensation neuroses constitute the majority or even a large percentage of post-traumatic functional disorders. In common with Strauss and Savitsky[3b] and Wechsler they reserve the term traumatic neurosis for a specific and infrequent syndrome first described by Horn[23] under the name of *Schreckneurose*, and subsequently discussed by Bernhard,[24] Libman,[25] and Sperling.[20] It is typical that it occurs only following a serious threat to life in such a situation that the patient has time to be aware of and terrorized by the impending disaster; accordingly it is frequent in war and earthquakes, and is seen occasionally in mining catastrophes and sea disasters, but almost never in the ordinary industrial and automobile accidents. Clinically the symptoms are usually those of an anxiety state, with particularly characteristic dreams in which the patient relives the traumatic situation. Unless complicated by secondary hysterical symptoms the condition tends to clear up spontaneously. The psychopathologic mechanisms differ from those in true hysteria, but are not fully understood as yet (Kardiner[11] and Fenichel[26]).

In a recent article Sands[27] classifies these syndromes in an analogous manner, namely as post-traumatic constitution, traumatic neurosis, traumatic hysteria, and malingering, but uses the term traumatic neurosis to apply to individuals who have recovered from a brain injury, frequently of the cerebral concussion type, and who do not show any neurologic or encephalographic signs, and yet show definite personality changes in the form of irritability, brooding, dizziness, and so forth. He reserves the term post-traumatic constitution for cases showing definite neurologic or encephalographic changes. In the same article this author presents an excellent study of brain changes due to head trauma. He finds that the post-traumatic sequelæ are due to loss of brain tissue, meningo-cortical adhesions, cicatricial contraction, collections of fluid in the meninges and interference with proper cerebrospinal fluid and lymphatic circulation. He advances evidence that significant brain injuries may occur without loss of consciousness.

Blau[28] has recently presented an exhaustive survey of post-traumatic behavior disorders in children. The author finds, in agreement with Strecker and Ebaugh[29] and Kasanin,[30] a marked similarity between these conditions and the postencephalitic behavior disorders. Typical are overactivity, restlessness, destructiveness, impulsiveness, assaultiveness, cruelty to animals, emotional instability, temper tantrums, truancy and delinquency. The prognosis in most cases was poor. The formal intellectual faculties were relatively well retained.

The therapy of the conditions under consideration requires little special mention. All contributors are agreed that the majority of post-traumatic psychoneuroses should be treated by exactly the same methods as in the usual non-traumatic cases. Compensation neuroses are always benefited by a lump sum settlement. The traumatic or terror neuroses tend to clear up spontaneously. The treatment of traumatic encephalopathy must be primarily palliative. Penfield[31] has relieved post-traumatic headaches through encephalography.

The possibilities of the prevention of post-traumatic psychoneuroses has aroused interest in recent years. Dershimer[32] comments on the work at the Fisher Body Company at Cleveland, where practically no psychoneurotic states have developed following the employment of a psychiatrist. The principal method of prevention is through the dissemination of knowledge concerning the causes of the psychoneuroses to employers and employees. FRANKLIN G. EBAUGH, M.D.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

JOSEPH C. BECK, M.D.,

ASSOCIATE PROFESSOR EMERITUS, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS MEDICAL SCHOOL,

AND

M. REESE GUTTMAN, M.D.,

INSTRUCTOR, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS MEDICAL SCHOOL.

PROGRESS IN RHINOLOGIC ASPECTS OF ALLERGIC DISEASE WITH ESPECIAL REFERENCE TO IONIZATION.

THERE has been a continuous and increasing appreciation of the rôle of allergy in the production and maintenance of otolaryngologic disease. This is reflected not only in the literature of the specialty but also in the diminishing attack upon the interior of the nose and paranasal sinuses. The incidence of allergy in otolaryngologic practice is higher than what is usually believed. Baum[1] reviewed a series of 2000 patients and found some 700 with nasal difficulty, 191 (27%) of which were allergic. Thus practically 1 out of every 4 patients in the otolaryngologists' office that has chronic nasal difficulty is allergic. Furthermore, if one considers the ratio of these allergic cases to the total number of patients studied (2000) one finds that 9.5% of all patients with a chronic complaint that seek aid of the otolaryngologist, or about 1 in every 10, are definitely allergic. A similar review of 1000 cases by Hansel[2] disclosed 142 cases of allergic disease in 324 patients with nasal disorder. Here about 40% or 2 in every 5 cases of nasal disease, are allergic and about 14% or 1 in every 7 patients routinely seen in practice, exhibits allergic phenomena. Undoubtedly if one considered acute illnesses, the percentages would be definitely reduced, but still of major importance. Kuhn, in a discussion of Vaughn's[3] paper, reported similar figures. It is obvious that the high incidence of allergic disease in routine otolaryngologic practice should be borne in mind, and this disorder must be considered whenever confronted by nasal symptomatology.

There have appeared a fair number of contributions[4–9] dealing with the general subject of nasal allergy and having as their main theme the frequency that allergy is encountered; the importance of considering it as a possibility in the differential diagnosis of nasal disease; the marked aid in diagnosis that is afforded by cytologic examination of the secretion; and the importance of proper diagnosis of the etiologic allergic factor. Many, further, dwell upon the futility of intranasal surgery except as a means of promoting drainage in secondary suppuration or relieving nasal obstruction. Watkins[5] especially calls attention to the fact that even multiple surgical operations frequently fail to give relief in allergic individuals except when infection with retention

is present as a complicating factor, and points to the frequent disappearance of polypi after proper allergic therapy.

As an aid in differentiating infectious from allergic nasal and paranasal sinus disease, the work of Buhrmester[10] must receive consideration. He found that in allergic disease the nasal secretions had a higher water content, averaging about 97% as compared to 90% found in infectious disease. As a consequence the total solids were 3% in allergic disease and 10% in infectious disease. There is present about three times as much total solids in infectious exudate as there is in allergic secretion. The protein content varied from 0.21% to 3.82% in allergic secretions as compared to the 3.45% to 16.23% found in infectious exudates. Similar figures have been reported by Mittermaier.[11] The ash in the total solids was much higher in the allergic secretions than in infectious exudate. The calcium was higher in infectious disease as compared to allergic disease averaging 11% and 9% respectively. The allergic secretions were found to have a higher pH or become more alkalin than the infectious exudates.

As an aid to the diagnosis of allergic disease, an intramucosal test similar to intradermal tests was described by Dean, Linton and Linton.[12] Appropriate extracts were either injected or applied to scratches made in the mucous membrane of the anterior end of the inferior turbinal. A positive reaction consisting of swelling, edema or even a wheal, would appear within 30 minutes, although a delayed reaction was also noted. In some instances, a positive intranasal mucosal reaction was obtained when the dermal test was negative.

Non-specific methods of treating nasal allergy continue to receive attention. Palmer[13] describes the effect of treating the nasal mucosa with phenol in 30 cases of nasal allergy and noted definite improvement in 80%. Histologic study of the mucosa after treatment disclosed an increase in the fibrosis with a decrease in the vascularity and edema of the tissue. Bernheimer[14] reported on the final results in 40 patients treated 3 years prior by Cutler and himself by the use of radium placed within the nose. He found 47% symptom-free, 22% had some sneezing, but no obstruction or rhinorrhea, 8% moderately comfortable, and 23% with little or no relief. There was no success in similar treatment of 12 patients afflicted with seasonal hay fever. By far the most important contribution to the literature dealt with the subject of ionization in the treatment of allergic disease. There were many contributions on the subject, dealing not only with the technique, but also with the histologic effects upon the nasal mucosa. Intranasal ionization, more properly called iontophoresis, has been brought to the attention of rhinologists and allergists as a worthwhile means of therapy in those cases in which specific immunization is difficult to effect or undesirable. Iontophoresis consists in the introduction of medical ions into the tissue by means of the galvanic current. It is nothing new, having been utilized over 30 years ago. Drugs or chemicals are forced into tissue by virtue of the fact that an aqueous solution of the drug or chemical contains a number of positively and negatively charged ions arising from the dissociation of the substance when placed into solution. If a constant direct or galvanic current is permitted to flow through the solution, the attraction of unlike charges

will cause the positively charged ions to move and collect at the negative pole and the negatively charged ions to move and collect at the positive pole. For example, a solution of sodium chlorid will have freely disassociated positive sodium ions and negatively charged chlorid ions. Upon being subjected to the galvanic current the sodium ions being positively charged will collect at the negative pole and the chlorid ions at the positive. By taking advantage of the migration of ions, heavy metals such as zinc, tin and cadmium have been utilized in therapeusis. Whether or not heavy metals are actually deposited in the tissues is still open to question. Lierle and Sage,[15] in a study of zinc ionization in the treatment of otorrhea, were unable to demonstrate that the zinc was actually deposited in the tissues of laboratory animals used in their experiment. Wenner,[16] on the other hand, was unable to demonstrate by means of chemical methods that zinc was deposited in the skin and cartilage of the ear of a rabbit. The source of the current utilized in the procedure may be batteries, which give a pure constant current. McFarland[17] described an inexpensive set that might be built. The source may also be from a rectifying circuit utilizing commercial current or it might be derived from various types of motor generator sets. In the use of motor generator and rectifying equipment it is essential that a smooth non-pulsating current be obtained. Warwick,[18] who originally aroused interest in this method of treatment in this country, advised that his special type of generator, together with a special electrode and a special electrolyte, were necessary for success. The composition of the electrode and the electrolyte were kept secret for a time. However, the informed opinion today holds that the special generator electrode and electrolyte are not essential to success. Any source of smooth galvanic current, ordinary zinc solution, and an ordinary zinc electrode will be effective.[19, 20, 21]

Technique. The technique as ordinarily employed consists in preliminary cocainization of the nasal mucosa. Gauze strips saturated in a 2% solution of zinc sulphate are packed into the nasal chambers. By means of a zinc electrode the gauze is connected to the positive terminal of a galvanic supply. The negative terminal is connected to a large sponge electrode placed over the arm or other suitable portion of the body. The current is slowly turned on and increased until the milliameter reads 10. This amount of current is permitted to act for 15 minutes and the current is then gradually decreased and shut off. Hollender[22] has described a new head band type of electrode that is easy of application and adjustment. Cottle[21] advises the use of a 2% zinc sulphate in 5% tragacanth jelly introduced into the nasal cavities by means of a syringe instead of packing with gauze strips. There is some objection to the use of the jelly in that it spreads to the upper portions of the nose so as to affect the Schneiderian membrane with the possibility of a resulting anosmia, which has occurred. At termination of the treatment the mucous membrane will be found to have been coated with a gray membrane. On the following days the nose is obstructed with a fibrinous jelly-like exudate which persists from 3 days to 1 week. The membrane should be permitted to be extruded spontaneously.

Tissue Changes in Iontophoresis. There is an increasing amount of study upon the effect of iontophoresis upon the treated tissue. There, however, is as yet no certain agreement as to the amount and permanence of tissue change subjected to ionization. Hollender and Gorin[23] find that there is an initial destruction of the surface epithelium with subsequent regeneration. The regenerated mucosa appears first as a squamous epithelium and then gradually assumes a pseudo-stratified structure within a period of 3 months. The cilia, however, remain absent while the subepithelial stroma tends to become more dense and infiltrated with lymphocytes that may persist for a much longer period of time. In but one section were they able to observe changes in the mucous glands. McMahon[24] stated that in the frontal sinuses and nose of dogs subjected to experimental ionization there appeared immediately after the treatment fragmentation of individual and large groups of cells and an infiltration of round cells from the surface down into the subepithelial structures. There was also apparent some separation of the tissue from the underlying periosteum in places. There was a return, however, within a period of 7 weeks of the epithelium to normal. Fibrosis of the subepithelial tissues became more noticeable as the animals were killed in increasing intervals from 18 hours to 7 weeks following the iontophoresis. In a report[25] made by the same investigator in a previous year there was found extensive immediate effects that were definitely destructive, in the nature of ballooning, fragmentation and loss of the surface epithelium associated with edema and partial disintegration of the subepithelial tissues as well as hemorrhagic extravasation from dilated and ruptured capillaries. In an extensive study of the regeneration of the nasal mucosa subjected to various insults, Boling[26] found that ionization destroyed the epithelium and produced leukocytosis and hyperemia; but had no noticeable effect upon the regeneration of the mucosa. The epithelium and glandular ducts regenerated from the basal cells and epithelial fragments left after the treatment. He also found that repeated ionization had no noticeable destructive effect upon the epithelium which regenerated from a previous ionization.

Smit,[27] in a similar study, found that immediately after ionization there occurred an acute inflammatory process with coagulation necrosis, sloughing of the epithelium, dilatation of the bloodvessels and neutrophil infiltration. These changes form an exudate membrane in the nose which also contains the sloughed epithelium. As the acute process subsides, the neutrophils are replaced by round cells which persist as long as there is any irritative process present. The denuded mucosa later becomes covered by stratified squamous epithelium. A return of normal ciliated epithelium was found to occur in guinea pigs 6 weeks following ionization and in one human biopsy 1 year after treatment. The bloodvessel walls show thickening while the glands and their ducts may evidence atrophy and metaplasia. As the reparative process continues, the submucosa becomes infiltrated with fibroblasts which are later converted to fibrous tissue. The contraction of the fibrous tissue may cause collapse of the venous spaces and retraction of the turbinates. New glands may appear by the ingrowth of epithelium. Cartilaginous necrosis may also occur. From these studies it is obvious

that extensive destruction of tissue is possible by this means of treatment. It is also apparent that there is tremendous regenerative power inherent in the nasal mucosa. The mucosal epithelium apparently has a tendency to return to normal, but the subepithelial fibrosis apparently persists for a long period of time and in addition there may be more or less atrophic changes in the glands.

From the clinical point of view the persistence of a fibrotic condition of the mucosa may not be without deleterious effects upon the patient. A contractile fibrous tissue change might well lead to ultimate decrease of blood supply and glandular atrophy. In addition late effects upon the nerves may eventuate in such unpleasant sequelæ as neuritis and anosmia, which have been observed in some instances. In all probability the intensity and extent of these tissue changes will be found to vary with the strength of the treatment that is administered. The problem is so to select the quality of the treatment as to effect the desired clinical relief without producing the progressive and irreversible histologic changes that might lead to disagreeable sequelæ.

The mechanism whereby relief is obtained following ionization has been the object of considerable speculation. Alexander[28] believes that a local non-specific desensitization occurs similar to that obtained by the use of various chemicals, diathermy, and electric cautery. The nasal mucosa has been found to be non-reacting for a period of time. However, the non-infrequent relief obtained by only treating one side might suggest a general non-specific desensitization such as is observed by the use of proteins or vaccines. That this may be a possibility is demonstrated by Chatjutin,[29] who was able to relieve nasal allergy by calcium ionization applied to the skin of the shoulder. Dean and his co-workers[12] noted many instances of positive reaction in the nasal mucosa to negative after ionization. Operative procedures within the nose had no effect in changing the reactivity of the nasal mucosa. Alexander[28] found that after ionization the topical application of a reagin caused little or no effect, in marked contrast to the effect prior to the treatment. Those patients in whom poor or no results were obtained by the therapy reacted within a short time to testing with reagins. However, the iontophoresis had no effect upon the presence of reagins in the blood nor upon the skin reactions.

The results in this type of therapy are varied. Warwick[18] reported practically 100% benefit in 40 cases, most of which were hay fever. Alden, in 1933,[30] relieved all of 19 patients suffering from autumnal fever by treating them during the attack. Nine had no recurrence during the following season, 8 had mild symptoms that were insufficient to cause them to seek aid and 2 had a marked recurrence. He also treated 41 patients in 1934 prior to the onset of the symptoms with protection to about half. Franklin[31] was able to render 50% of his hay fever patients and 60% of his hyperesthetic rhinitis cases free from symptoms by means of iontophoresis. Hollender[22] secured similar relief in about 50% of his cases. Hurd[20] states that in cases of hay fever his percentage of good results have been high and that 70% of his cases of hyperesthetic rhinitis have been rendered symptom-free. He, however, gives no table of statistics beyond the statement noted. Ramirez[32] was unable to obtain any noteworthy relief in 100 cases of

hay fever treated by ionization. On the other hand, 25 cases of vasomotor rhinitis experienced relief in the majority of cases. House and Gay[33] studied this form of treatment in 20 cases. In 5 non-allergic patients 3 were improved, 1 unimproved and 1 made worse. In 15 allergic patients but 3 were improved, 7 were unimproved and 5 were worse. They concluded that ionization was not worthy of consideration in allergic cases. Alden[34] compiled the results of a number of observers. A total of 700 cases was tabulated. In 416 cases of uncomplicated hay fever, complete relief was obtained in 63% and total failure in but 8%. In a group of 27 patients with asthma, 37% were relieved. In 73 patients with allergic rhinitis complete relief was afforded in 47%. Tobey[35] stated that desensitization was the method of choice although ionization can control the symptoms if instituted after the onset of the attack. It is apparent that ionization is a useful addition to the therapeutic armamentarium. It is also apparent that its exact sphere of utility has not as yet been definitely determined.

Our own experience in the last 2 years has definitely impressed us with the symptomatic relief that may be obtained in about 75% of the cases of hyperesthetic rhinitis that have come under our observation. One may not speak of ionization as a cure for this disorder; but the prolonged palliation that may be obtained certainly bespeaks its usefulness. In hay fever our experience has not been so striking. In but few of our cases, treated prior to the onset of the symptoms, were definitely discernible results obtained. Some better results were manifested in its utilization after symptoms had appeared. Here a few patients were rendered symptom-free; a larger number showed definite amelioration, while the greatest majority experienced little or no relief. Ionization must at the present time be viewed as a valuable adjunct to other accepted methods of treating hyperesthetic rhinitis and to a lesser degree hay fever.

Joseph C. Beck, M.D.,
M. Reese Guttman, M.D.

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Studies of the Pituitary of Thyroidectomized Rats.—Isolde T. Zeckwer (Laboratory of Pathology, University of Pennsylvania). When thyroidectomy is performed in young immature rats, histologic changes occur in the pituitary which have been discussed elsewhere. "Thyroidectomy cells" occur which consist of cells containing a large amount of hyalin material. Acidophils are decreased in number. Cretin rat pituitaries contain an abundance of thyrotropic hormone, but when injected into guinea-pigs do not cause as great an increase in absolute weight of the guinea-pig thyroid as do normal rat pituitaries. However, the dwarfed cretin rat has available for each gram of its body weight a little more hormone than the normal rat.

The "thyroidectomy cells" are not castration cells, because the cell granules are different, and because they occur in abundance in pituitaries of male rats in which gonad atrophy has not occurred.

Collin and Hennequin (*Compt. rend. Soc. de biol.*, **121**, 81, 1936) have reported that stimulation of the cervical sympathetic nerve in rabbits causes an increase in the acidophil granules in the pituitary, while excision of the superior cervical ganglion causes rapid and nearly complete loss of acidophil granules. Until experiments have been completed to determine whether injury to sympathetics could be a factor in our experiments, interpretation that the decrease in acidophils in cretin rats' pituitaries may account for the stunting of kidney growth and body weight will be regarded as only tentative.

The changes in proportion of cell types in the cretin rat pituitary do not prevent the growth of adrenals and gonads in the male.

The present experiments concern only rats. There are apparently species differences in the reaction of the pituitary to thyroidectomy.

Experimental Efforts to Detect Secretion of Inulin by the Tubule of the Mammalian Kidney.—P. A. Bott, B. B. Westfall, and A. N. Richards (Laboratory of Pharmacology, University of Pennsylvania).

Earlier work by the authors, by Smith and Shannon and by Van Slyke and collaborators has furnished basis for the belief that inulin, injected intravenously into mammals, is excreted by the kidney solely by glomerular filtration. Further evidence concerning the possibility that inulin is in part secreted by the mammalian tubule was desired. In a variety of experiments with dogs and rabbits, inulin was added to blood which flowed through the renal vessels at pressures low enough to prevent glomerular filtration. After varied intervals normal blood containing no inulin was substituted at high pressure and a specimen of urine collected. Only traces of inulin were found in it. In every experiment to the inulin-blood was also added one of those substances which are now believed to be secreted into the urine by the tubule (phenol red, neutral red or diodrast). Each of these was found in the urine in relatively large amounts. Hence under conditions which permit tubular secretion of phenol red and other substances, inulin is not secreted by the mammalian tubule.

On the Nature of Intestinal Absorption of Amino Acids.—Rudolf Höber and Josephine Höber (Laboratory of Physiology, University of Pennsylvania). By a number of investigations it has been established that a good many organic substances—provided that they are lipoid-insoluble—enter cells and tissues the more rapidly, the smaller the volume of their molecules (m.v.). An interesting exception to this rule has been disclosed in comparing the entrance of amino acids into physiologic structures with that of other solutes of similar molecular volume. It appeared that the amino acids pass through the surface of cells and tissues, *e. g.*, the surface of red cells or of muscles, with remarkable slowness.

This striking behavior can be explained on a purely physicochemical basis. Experiments on the diffusion of a number of organic substances across collodion membranes have shown that the amino acids similarly penetrate these artificial membranes at a slower rate than would be concluded from their molecular size. The reason is that the "zwitterions" of the amino acids are strong electric dipoles, which, exerting a pull on the surrounding water dipoles, form a water shell preventing them from moving at the expected higher rate.

Then we became aware of still another irregular behavior of the amino acids when we studied their penetration of the intestinal wall of the rat. However, here the observed rates of absorption have not been found to be too low, but, on the contrary, they are much higher than physicochemically demanded. For instance, in comparing the absorption of some amids differing in their m.v., the intestine reveals the properties of an inert diffusion membrane, where penetration occurs parallel to the diffusibility of the solutes, *e. g.*, succinamid m.v. 126, per cent absorbed 3; lactamid m.v. 98, per cent absorbed 52; acetamid m.v. 69, per cent absorbed 78.

The behavior of amino acids is strikingly different, *e. g.*, the m.v. of alanin and malonamid seem to be nearly the same, 98 and 104, but, due to the shell of water dipoles, the effective volume of alanin is by far the greater. Consequently, one would expect the absorption rate of malonamid to surpass that of alanin. But the opposite is true: alanin per cent absorbed 59, malonamid 26. Or: succinamid m.v. 126, per cent absorbed 9, asparagin m.v. 134, per cent absorbed 46.

On the basis of these and other statements we arrive at the result that, as regards their intestinal absorption, the amino acids are privileged in a similar manner as, according to former experiences, some hexoses are.

Absorption of Glucose from the Human Small Intestine.—W. Osler Abbott, W. G. Karr, and T. Grier Miller (Gastro-intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania). In studying the absorption of simple sugars certain steps in the process have been neglected. One of these is the relationship between the concentration of the glucose in the stomach and that in the intestine. Data are presented to show that, irrespective of the volume or the glucose concentration of the solution ingested, the concentrations found in the jejunum and ileum range from 0 to 5%. This confirms in man observations previously made in animals. The fall in concentration between the gastric cardia and the jejunum has been studied by using two multilumened tubes through which sets of specimens could be simultaneously aspirated from five selected points in the stomach and duodenum at stated intervals. Analyses show a wide range of concentration at these points but rarely more than 5.4% of glucose in specimens from near the ligament of Treitz. Further data show that a very rapid inflow of fluid occurs from the walls of the stomach and duodenum. This in conjunction with the predominantly segmental rather than peristaltic action of the duodenum accounts for the sharp fall in concentration by which the small intestine, even as close as 30 to 40 cm. from a stomach containing strongly hypertonic glucose, is provided with a relatively isotonic solution. Feeling from these studies that the normal glucose concentration of intestinal contents is below 5.4% (isotonic), we made absorption studies in segments of jejunum and ileum isolated by distended balloons. Placing 50 cc. volumes of 0.67 to 5.4% glucose solutions in these segments for 15-minute intervals, then emptying and washing with saline, the amount of glucose absorbed could be determined. The results show that the amount of absorption increases with the concentration.

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